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ULCERATION IN THE DIGESTIVE TRACT OF THE DOG FOLLOWING INTRACRANIAL PROCEDURES

PRELIMINARY STUDY

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The Balfour Lecture delivered by Dr. Cushing [1] at Toronto in 1932 stimulated the interest of my associates and me in the routine examination of the gastro-intestinal tract at the death of all the animals in our experimental series or at the termination of the experiment. Our comprehensive program consists of placing mechanical lesions in various parts of the brain-stem in a systematic investigation of the functions of the brain-stem, with particular reference to exact anatomic localization. Our procedure is to maintain preparations to the "chronic" state so as to interpret better the effects of deprivation and to allow time for actual degeneration of the anatomic systems injured. At the beginning cats were used largely; however, recently we have shifted practically entirely to the use of dogs because of the greater ease of keeping dogs in good health under laboratory conditions. Accordingly, this report consists of observations on changes in the digestive tract encountered in a preliminary series of dogs, with occasional comments regarding the series of cats.

REVIEW OF THE LITERATURE

EARLY OBSERVATIONS

Schiff [2] began his discussion of the relation of pathologic changes in the gastro-intestinal tract to injuries of the central nervous system, in a somewhat abbreviated form as follows:

> In the study of human pathology it has long been recognized that certain chronic diseases of the brain and especially disturbances at the base are associated with particular disorganization of the mucosa of the stomach, the disorganization being characterized by hemorrhagic spots and partial softening. Most of these observations have been made on infants; it is rare that the lesions are present in an adult.

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1. Cushing, H.: Surg., Gynec. & Obst. **55**:1, 1932.

2. Schiff, M.: Leçons sur la physiologie de la digestion, Florence, H. Loescher, 1867.

Kammerer was the first to attract attention to the frequent association with certain cerebral lesions of this special form of softening of the stomach, numerous examples of which are presented from his observations. After his work Audral and Rokitansky confirmed these facts by a larger series of observations.

The connection which exists between these distant lesions has been perfectly grasped by supposing that they were transmitted by the nervous system. The great sympathetic nervous system not having at that time been stripped of its rôle of an independent system, investigators were forced in good faith to place the path of this curious transmission in the pneumogastric nerves.

But as soon as knowledge of the functions of the nervous system was increased by new facts, the observations which I have just cited lost the mystery which enveloped them, and attempts were made to reproduce artificially the hemorrhagic softening of the stomach by producing various lesions in the central and the peripheral nervous system.

Schiff encountered in the rabbit and dog bloody stasis and softening of the mucosa of the stomach following hemisection of the brain stem at the level of the optic layer and cerebral peduncles, transverse section of the lateral half of the annular protuberance, partial lesions in the pons, hemisection of the caudal portion of the medulla and hemisection of the cervical region of the cord. No such disturbance occurred in the stomach of animals after section made "in every manner across the cerebral hemisphere, the corpora striata and the superficial layers of the cerebellum and after oblique cuts across the quadrigeminal bodies and sections of the lower (lumbar) portion of the cord." The evolution of the process, according to Schiff, was somewhat as follows:

The mucosa of the stomach becomes uniformly reddened, and then one sees patches of round areas of intense redness which soon become dark brown and then blackish brown. At the same time that a patch becomes brown its base is raised and takes on a loose consistency. The substance of the patch is softened and becomes detached by the passage of food, which sometimes remains adherent. The detached patch leaves a superficial erosion with sharp borders. At this period the disorganization sometimes stops, especially in the rabbit, but in the dog the erosion once produced penetrates more deeply, reaching the submucosa and the muscular tunic itself. I have never seen complete perforation effected in the intestine, but it sometimes happens that the serous coat of the stomach is perforated, an accident which is always fatal because of the acute peritonitis. The ulcers examined at autopsy have the form of a funnel with the large diameter turned toward the mucosal side. The gastric glands in these conditions contain no well developed peptic cells but only nuclei and small nucleoli. The intestinal hyperemia is confined more specifically to the villi.

In the series of Schiff these alterations occurred invariably in rabbits by the fourth day, reaching their maximum effect by the eighth day. In dogs they never occurred under any circumstance if the animal was fed a soft diet (meat and milk), but they were of frequent occurrence if bones were fed. Schiff accordingly pictured the central lesion as lowering the resistance of the gastric mucosa to rough food, and he was emphatic that the underlying mechanism responsible for this lowered

resistance was directly due to vasoconstrictor paralysis. He developed his argument with great experimental detail, pointing out with clarity that the vasoconstrictor pathway to the stomach was the sympathetic outflow rather than the vagus nerves, as had formerly been postulated. His enthusiasm for the theory that "neuroparalytic hyperæmia" was the direct cause of the gastro-intestinal changes following ingestion of rough food seemed not to have been shaken by the fact that even in his hands bilateral section of the splanchnic nerves or bilateral removal of the celiac ganglions (in the absence of traumatic handling of the gastro-intestinal tract) failed to precipitate any gastro-intestinal changes in the rabbit or in the dog even when the animal was fed rough food.

Ebstein [3] obtained changes in the gastric mucosa of rabbits and dogs after traumatic hemorrhagic lesions in the region of the superior colliculi, injection of a drop of chromic acid into the substance of one superior colliculus, hemisection of the medulla, hemisection of the cervical portion of the cord and injury of the lumbar region of the cord. He failed to obtain any changes by placing lesions or injections of chromic acid deeper in the tissue of the cephalic portion of the midbrain at the relative position that Schiff found most effective in the precipitation of changes. The hemorrhagic spots appeared earlier after operation than they did in the investigations of Schiff. Ebstein also stated that the hemorrhage was preceded by localized edema. Ebstein's results are hard to evaluate because he obtained similar changes in dogs after lesions of the labyrinths, section of the sciatic nerves and any procedure that caused death from asphyxiation.

Brown-Séquard [4] described an instance of perforated gastric ulcer in a dog following cautery of the "surface of the brain" and also gastric hemorrhage following lesions which involved "a point of the pons Varolii which is found at the level of the insertion of the middle cerebellar peduncle." Unlike Schiff, he failed to obtain gastric changes with lesions of the medulla. He agreed with Schiff that the ulcerations were not mediated via the vagus nerve, but he stated emphatically that the mechanism responsible was not vasomotor paralysis. He also seemed to question whether the "softenings" were preceded by hemorrhage; however, this point is not clear from his short discussion. It would seem at least that he encountered "softening" in the absence of hemorrhage.

RECENT OBSERVATIONS

Ivy [5] observed petechial hemorrhages and superficial erosions of the mucous membrane of the fundus and pylorus in ten dogs dying

3. Ebstein, W.: Arch. f. exper. Path. u. Pharmakol. **2**:183, 1874.
4. Brown-Séquard, C. E.: Progrès méd. **4**:135, 1876.
5. Ivy, A. C.: Arch. Int. Med. **25**:6, 1920.

of shock and symptoms of increased intracranial pressure following ablations of the cerebral hemispheres. A few of his dogs that lived for some time with injury of the underlying thalamus passed undigested food and liquid paint-colored feces containing arterial blood before death. In these animals mucosal hemorrhages were noted in the stomach only.

Burdenko and Mogilnitzki,[6] in a large series of dogs with mechanical lesions placed in the hypothalamic region, encountered extravasation of blood, hemorrhagic erosions and erosions unassociated with hemorrhage in the stomach and duodenum. They visualized the process as being largely one of localized dilatation and bursting of mucosal blood vessels, with subsequent digestion of the necrotic spots by the digestive juices. They recognized, however, that the process is not purely vasomotor but a general disturbance of all the chemicophysical processes involved in the gastro-intestinal functions. They stressed particularly disturbance in trophic function. It would also seem that they suspected that the formation of craters could take place in the absence of hemorrhage, since they stated that hemorrhage occurred only when the corpus Luysi was involved whereas craters were observed when this nucleus was uninjured.

Cushing [1] has described his clinical experiences in which definite antemortem gastro-intestinal changes occurred directly after intracranial operations, and he has pointed out with excellent case histories the frequent association of gastro-intestinal disturbances and tumors of the hypothalamic region. In all his cases bleeding into the lumen and into the gastric mucosa was prominent. After presenting his material and reviewing the clinical and experimental literature, Cushing suggested that the gastro-intestinal changes were mediated via the vagus nerves. He presented convincing evidence [7] that the central mechanism of the vagus nerves is represented in the brain-stem as far cephalad as the hypothalamus. He pointed out with emphasis that the lack of clinical information regarding the occurrence of pathologic changes in the gastro-intestinal tract following intracranial involvement is probably due to two factors: The gastro-intestinal tract has not been examined at autopsy, and knowledge is lacking as to the presence and extent of pathologic changes occurring after cerebral accidents and operations which heal after the clearing of the central lesion. That the latter occurs was clearly demonstrated at the meeting of the Harvey Cushing Society in St. Louis in 1934, at which reports of cases collected by various neurosurgeons in the country were presented. Particularly striking were several cases in which blood was vomited shortly after intracranial

6. Burdenko, N., and Mogilnitzki, B.: Ztschr. f. Neurol. u. Psychiat. **103**: 42, 1926.

7. Cushing, H.: Proc. Nat. Acad. Sc. **17**:163, 1931.

operation and complete recovery followed, as well as other cases in which bleeding occurred into the lumen of the stomach with no demonstrated change in the mucosa at autopsy.

Watts and Fulton [8] and Hoff and Sheehan [9] in Fulton's laboratory have clearly demonstrated the occurrence of gastric and duodenal erosions following lesions of the anterior portion of the hypothalamus in the monkey, the work of the latter investigators being particularly convincing because the animals were killed while they were in fair physiologic condition.

EXPERIMENTAL INVESTIGATIONS

METHODS

Preoperative Care of the Animals.—Small or medium-sized, well nourished dogs were selected. To each animal was administered on a fasting stomach one hexylresorcinol crystoid (0.2 Gm.) for each kilogram of body weight. This medication essentially frees the intestinal tract of Ascaris, tapeworms, pinworms and hookworms, with which the dogs of this locality are heavily infested. Ridding the dogs of worms is necessary in order (1) to obtain postoperative chronicity, since dogs are likely to succumb rapidly to infestation with worms after a major lesion of the brain stem as they do to malnutrition or to infection of the respiratory tract and (2) to prevent hemorrhage due to worms in the lower part of the small bowel and in the large bowel, which would complicate the hemorrhagic picture which follows certain lesions of the brain stem.

Anesthesia.—As Professor Fulton [10] has pointed out, the barbiturates are excellent anesthetics for use in experimental surgical procedures on the brain. Until the present, we have used almost exclusively pentobarbital sodium, administered intraperitoneally, because of the more rapid recovery from its effects than from those of amytal or dial. Surgical anesthesia is maintained with one administration (40 mg. per kilogram of body weight) long enough for operation, and at the same time the brain is ideally relaxed for purposes of manipulation and visibility.

Soon after we began the examination of the gastro-intestinal tract of the animals in our series, occasional characteristic single punched-out defects of the mucosa were encountered in the stomach and bowel. The possibility that the defects were due to the lesion of the central nervous system was soon rejected, because they occurred singly and in the absence of any other gastro-intestinal manifestations as well as after any type of lesion of the brain stem. That these defects were due to puncture of the gastro-intestinal wall by the needle in administering the pentobarbital sodium was soon suspected from the fact that in nearly every instance the protocol revealed that a second injection was necessary to induce surgical anesthesia. That this was true was readily verified by injecting the drug into the wall of the bowel under direct visibility through a laparotomy opening. At

8. Watts, J. W., and Fulton, J. F.: Ann. Surg. **101**:363, 1935.

9. Hoff, E. C., and Sheehan, D.: Am. J. Path. **11**:789, 1935.

10. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

our suggestion, Dr. G. H. Kistler [11] has subsequently made a more detailed study of the process involved, utilizing the direct visibility method and has found that the same effects are produced by other barbiturates.

The incidence of such punctures was rather high in the early part of the series, the stomach being involved more often than the bowel. This was undoubtedly due to the early procedure of feeding the animals just before operation. A full stomach is tolerated well when the animal is under the effect of barbiturates, and we accordingly believed that it was good preparation for the immediate postoperative period. Probably also we did not use great care in the intraperitoneal injection, being under the impression that the gastro-intestinal wall was rather impervious to a needle.

In spite of occasional puncture of the gastro-intestinal wall, even when care is taken, we continue to utilize the intraperitoneal route for the administration of pentobarbital sodium. Injection by the subcutaneous and intramuscular routes does not yield as uniform anesthesia for a given dose as does intraperitoneal administration. This is due, no doubt, to variability in the rate of absorption from these routes. The difference is more pronounced with the use of pentobarbital sodium than with that of amytal or dial because of the more rapid recovery after administration of pentobarbital sodium. With subcutaneous or intramuscular injection elimination is already well under way before all of the dose has been absorbed, since injection by these routes often entails a second administration, and even then the degree of narcosis is not as predictable as when more rapid and uniform absorption occurs. From the standpoint of a consistent, rapid maximum effect per dose, the intrapleural route is even more satisfactory for the administration of pentobarbital sodium than the intraperitoneal; however, it has not been adopted because of pneumonitis which occasionally followed intrapulmonary injection and always resulted in the death of the animal.

The whole gastro-intestinal tract is susceptible to puncture with a needle unless great care is taken. The accompanying photographs (figs. 1 and 2) demonstrate instances of puncture of the body and the pylorus of the stomach which have occurred in our series since we began to exercise particular care with the injections. The punched-out defect, with the cavity clear or filled with necrotic débris and the adjacent edematous border, was readily identified as an acute injury due to pentobarbital sodium. Involvement of this type stands out in marked contrast to the normal gastro-intestinal tract or to the more generalized changes (figs. 4, 12 and 13), to be described later, which in certain instances follow lesions of the brain stem.

It is noteworthy that the gastro-intestinal tract tolerates such large defects as are shown in the photographs with no apparent dysfunction in the digestive processes. We have yet seen no clearcut instance of delayed healing or of extension of such a defect, in spite of the use of vagotomy and sympathectomy.

Placing the Lesions.—The problem from the beginning was to find the method of placing lesions that made them least susceptible to hemorrhage, edema, etc., thus allowing the maximum chance for the permanent recovery of the animal. The knife method was soon discarded because of the extreme likelihood of hemorrhage and edema. The cautery method was likewise discarded, because of the devitalized tissue left behind and the associated adjacent edema. The blunt dissection method was finally adopted. In this method the large blunt probe was first used, then the blunt blade and finally the small blunt probe. The latter procedure consists of

11. Kistler, G. H.: Am. J. Physiol. **105**:63, 1933; J. Lab. & Clin. Med. **20**:155, 1934.

using the blunt end of a no. 8 milliner's needle, which is held in a needle holder for purposes of manipulation. Another method, which holds promise for use in certain experiments but which has not yet been used for more than preliminary tests, is the blunt punch suction method. With a square glass tube attached to a suction apparatus, the complete caudal half of the midbrain has been removed, leaving the brain stem caudally and anteriorly with an intact blood supply.

Fig. 1.—Mucosa of the body of the stomach, showing a healing defect in the upper left hand portion and immediately above it a large penetrating ulcer with a broad elevated edematous border. The first ulcer was incurred three weeks prior to termination by the administration of pentobarbital sodium as an anesthetic, at which time the vagus nerves were cut above the diaphragm. The second ulcer was incurred twenty-four hours before termination of the experiment when pentobarbital sodium was again administered. In the lower right hand portion are spontaneous small ulcers of the type that occur relatively frequently after vagotomy.

Operative Approaches to the Brain Stem.—The hypothalamic region is approached by retracting the temporal muscle, removing the underlying bone and elevating with a spatula the temporal pole, thus exposing with excellent visibility the hypothalamus, which is bounded ventrally by the hypophysis, anteriorly by the

cephalic edge of the optic chiasm, anterodorsally by the optic tracts, posterodorsally by the cerebral peduncles and caudally by the anterior limit of the interpeduncular fossa. With the needle bent at an angle, any desired lesion can be placed with excellent surface visibility and with a minimum of resultant bleeding.

The midbrain and pons are approached by elevating the occipital pole unilaterally or bilaterally as desired, thus exposing the dorsal surface of the corpora quadrigemina. A straight milliner's needle is then projected into the brain stem at the position and to the extent desired and pulled slowly in the required direction. The falx is a convenient guide for the location of the midline.

Fig. 2.—Mucosa of the proximal portion of the pylorus, showing a large punched-out ulcer, which was incurred when pentobarbital sodium was injected a week before termination of the experiment. The edema of the edges has practically subsided; the necrotic material has sloughed; the base is well vascularized, and healing has begun.

The medulla is approached by removing the occipital bone dorsal to the foramen magnum after separating the muscles of the neck along the midline. The caudal portion of the vermis is then lifted on a spatula, exposing the floor of the fourth ventricle. With a needle bent at the desired angle any type of lesion can be placed under direct visibility in the medulla or the lower portion of the pons. There are certain limitations in the placing of lesions in the medulla because of involvement

of the respiratory mechanism. Certain of the precautions referable to the pons and the upper part of the medulla have been previously described.[12] The limitations referable to the lower portion of the medulla will be described in detail in a subsequent paper.

Postoperative Care of the Animals.—Immediately after operation the animals were placed in heated incubators until heat regulation was resumed.

Early in the program we administered saline solution immediately after operation even when preoperative feeding was pursued and gave milk and water freely the following day. We have now, however, completely reversed this procedure; food is withheld for from twelve to twenty-four hours before operation, and fluid is not administered until the second day after operation and even then is restricted for several days.

Examination of the Tissues.[13]—At the death of the animal or the termination of the experiment, the block of the brain stem containing the lesion was cut serially, and suitably selected sections were stained for cells and adjacent sections for fiber tracts. This method allowed for precise determination of the location and extent of the lesion and in "chronic" tissue, the determination of degenerated fiber tracts and cell groups as well.[14]

RESULTS

Digestive Tracts of Dogs on Which No Operation Was Performed.—The digestive tracts of nearly 150 dogs used in the student laboratory were examined carefully as a group of controls with which to compare the changes encountered after intracranial procedures.

In 10 or 12 instances characteristic shallow, round hemorrhagic craters were observed in the body of the stomach and in the pylorus. These occurred in slightly thin animals having signs of infection of the respiratory tract. Similar shallow craters have been seen in undernourished cats. In no instance was any sign of a gross defect encountered in the mucosa of the duodenum.

Hyperemic spots, rather few and widely separated, were encountered occasionally in the body of the stomach. Hemorrhagic areas were never present. In no instance was free blood encountered in the lumen of the stomach. A point to be remembered is that the mucosa of the body of the stomach is usually readily distinguished from the fundus and pylorus, since it exhibits moderate generalized arterial hyperemia whereas the fundus and the pylorus are blanched. There is no evidence in such a stomach of blotchy hyperemia. In the absence of worms, hyperemia of the sort bordering on hemorrhage or bleeding into the lumen has never been encountered in the duodenum or the rest of the small bowel.

12. Keller, A. D.: Am. J. Physiol. **96**:59, 1931.

13. Methods for the routine staining of fibers and cells in the same tissue, in paraffin as well as in pyroxylin, have been developed as a direct result of this program during the past three years, largely through the efforts of Mr. W. K. Hare. Dr. James O. Foley, of the department of anatomy, offered crucial suggestions and gave assistance.

14. Keller, A. D., and Hare, W. K.: Arch. Neurol. & Psychiat. **32**:1253, 1934.

Localized hemorrhages with bloody intestinal contents are, of course, frequently associated with parasitic infestations.

Preliminary Series.—The series on which this report is based consisted of approximately 200 dogs having experimental lesions of the brain stem of the following types of distribution: 6 massive prechiasmal (ventral); 33 extensive transverse chiasmal (fig. 3); 20 less extensive hypothalamic (unilateral, of the ventral third, etc.); 30 massive hypothalamic (amounting to complete removal of the hypothalamus); 15 longitudinal thalamic and hypothalamic; 35 midbrain (hemisections, complete transections, sections of the lateral quarter and longitudinal sections); 35 of the pons and upper part of the medulla, and 25 cerebellar. In addition to the series just enumerated, mention will be made of a few instances of unilateral removal of the anterior portion of the cerebral hemisphere as well as of the intraventricular injection of blood.

Bleeding into the Lumen of the Gastro-Intestinal Canal Associated with Hyperemia or Hemorrhage of the Mucosa.—Hemorrhagic states ranging from pronounced blotchy hyperemia of the body of the stomach with bleeding into the lumen to more marked lesions in which the hyperemia had progressed to localized hemorrhages in the mucosa were encountered in certain instances. As a rule, the pylorus remained blanched, as did the fundus; however, in a few cases the pylorus was somewhat reddened in spots. When the fundus was involved it was never to as marked a degree as the body, the line of separation of the fundus and the body being readily detectable. The mucosa of the body adjacent to the pylorus was always more hyperemic and hemorrhagic than the portion near the fundus (fig. 4).

In no instance were gross or histologic evidences of crater formation associated with the hemorrhagic states; nevertheless, certainly, it would seem that bleeding in most instances occurred at well delimited points, as judged by the characteristic localized blotchy hyperemia (fig. 4), the localized hemorrhagic areas (fig. 5) and the frequent localized, attached blood clots (fig. 6 *A*).

Usually hyperemia of the stomach was associated with that of the mucosa and with bleeding into the lumen of the duodenum. More frequently the involvement of the duodenum was generalized, beginning abruptly just beyond the pyloric sphincter (fig. 4). Occasionally the hyperemia occurred in longitudinal patches, as though the mucosa had been thrown into longitudinal folds, the crests of which alone were involved.

The histologic picture in the hemorrhagic states ranged from slight localized engorgement of surface capillaries with blood on the surface adjacent to the lumen (figs. 6 *A* and *B*) to marked localized engorge-

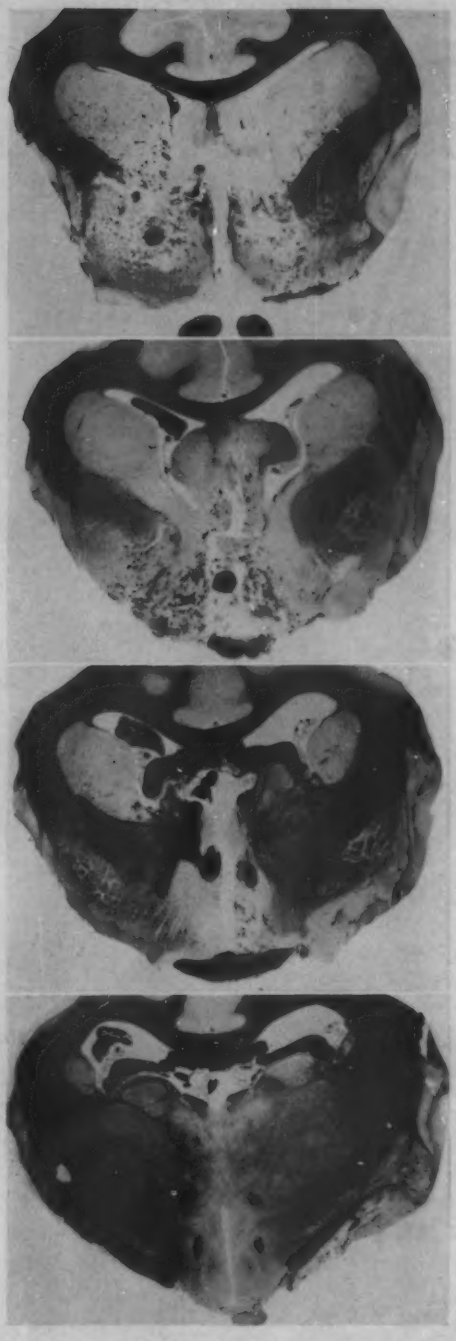

Fig. 3 (dog 27 B).—Four sections of the brain taken from the series showing the location and extent of the lesion. Complete maceration of the prechiasmal area, with encroachment of the lesion on the anterior portion of the hypothalamus, and the intact hypothalamus at the level of the infundibulum are evident. The ventral portion of the third ventricle is free from blood, and the hypophysis is undisturbed.

ment of surface capillaries and localized hemorrhage (figs. 5 and 7). Although usually the engorgement or hemorrhage of the capillaries was confined to the mucosal surface, occasionally capillary engorgement was seen to extend along the length of the capillaries to the muscularis (fig. 7). The cellular elements of the mucosa showed as a rule no signs of change, appearing normal in spite of being in instances completely surrounded by hemorrhage (central area of the section, fig. 8). The only changes noted were: a tendency for the basophilic cells surrounding

Fig. 4.—The stomach and duodenum of dog 406, after fixation in Klotz' fluid, showing blotchy hyperemia of the body of the stomach, the more intense areas of which range from 1 mm. to several millimeters in diameter. The fundus and pylorus are readily distinguishable from the body. The hemorrhagic appearance of the duodenum is evident.

a hemorrhagic area to stain more heavily than those farther away (fig. 15) and massive disappearance of all cellular elements, which would seem undoubtedly to be the result of depletion of the blood supply due to the neighboring hemorrhage (left portion of the field, fig. 8). In such areas it is noticeable that the basophils always precede the acidophils

in the order of their disappearance. In no instance has there been any evidence of sloughing or digestion of the areas of hemorrhage.

In the duodenum, as shown histologically, the picture ranged from engorgement of the capillaries of the villi to massive surface hemorrhage of the mucosa. We have not yet seen the hemorrhagic process

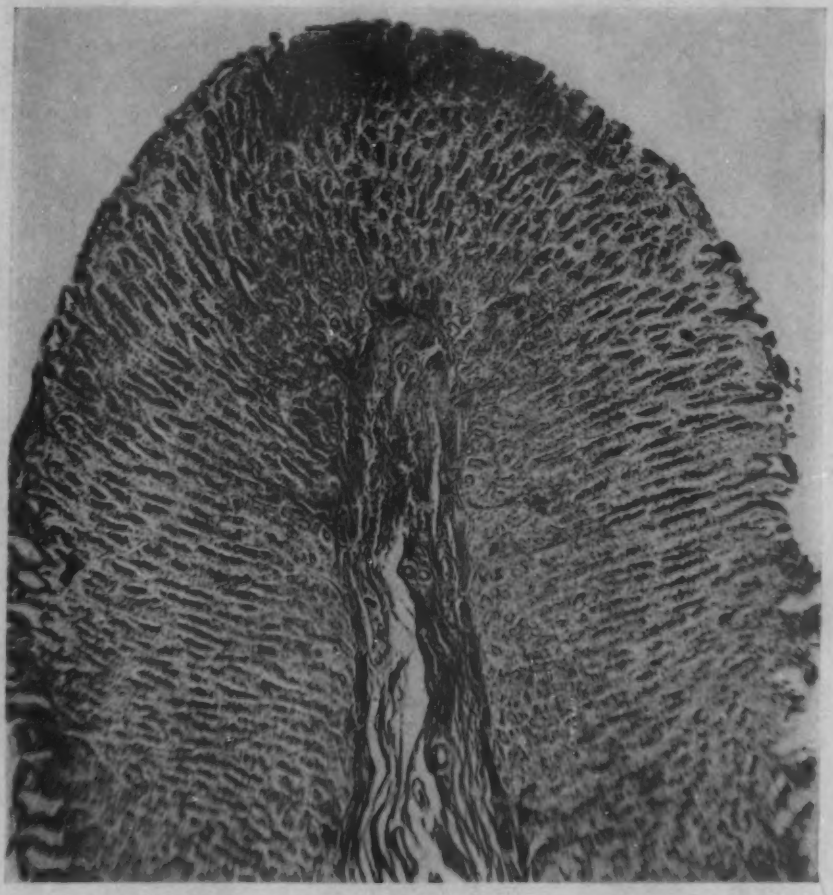

Fig. 5.—A superficial, well delimited area of hemorrhage on the crest of a mucosal fold of the stomach of dog 27 B. The absence of blood in the vessels shown elsewhere in the picture is evident.

extend through the entire mucosa to the muscularis. In both the stomach and the duodenum the absence of cellular reaction about the pathologic process has been conspicuous.

Changes in the rest of the small bowel and in the large bowel certainly occurred; however, I propose not to concern myself with these

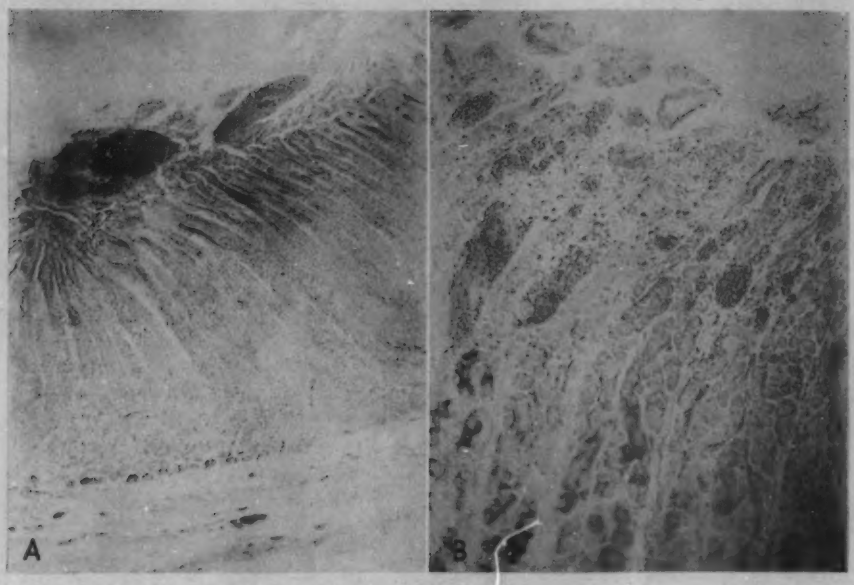

Fig. 6 (dog 85 B).—*A* is a photomicrograph of a section of the stomach, showing slight localized surface engorgement and blood clots attached to the surface bordering the lumen, and *B*, a photomicrograph taken under higher magnification of another area of the same stomach showing the engorged unbroken vessels near the surface bordering the lumen. The constricted capillaries between the cords of cells leading from the involved area to the muscularis and the normal-appearing mucosal cells surrounding the area are evident.

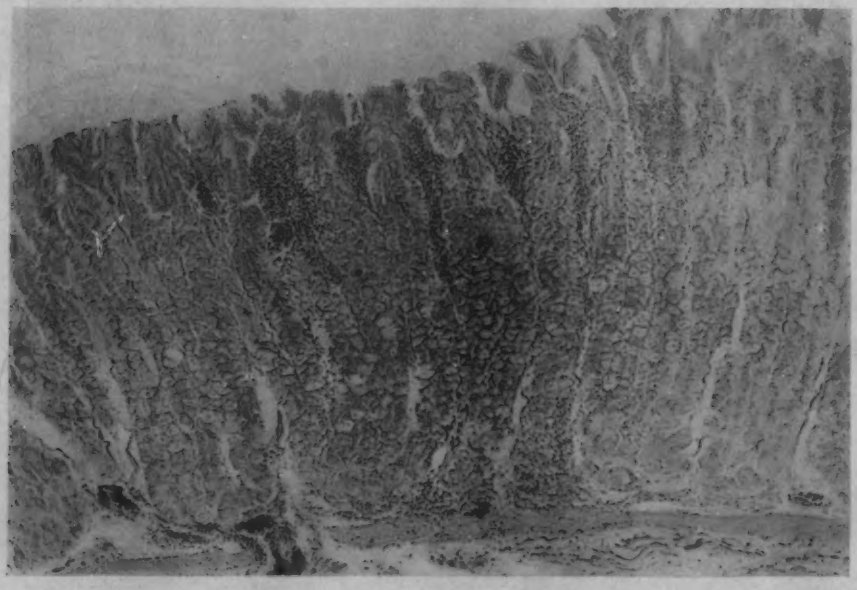

Fig. 7.—Photomicrograph of a well delimited hyperemic area from the stomach of dog 27 B. Blood remains in the capillaries through their entire course to the muscularis.

aspects further than has already been reported,[15] because the general pattern of occurrence is not yet sufficiently distinct to us.

That the hyperemia and bleeding occurred ante mortem is evident from a study of the gross and histologic changes. The occasional early vomiting of blood and the bloody mucoid diarrhea which frequently appeared soon after operation indicate that the precipitating process was progressive, beginning immediately with the onset of light anesthesia, and that, accordingly, it was not the result of "slow death."

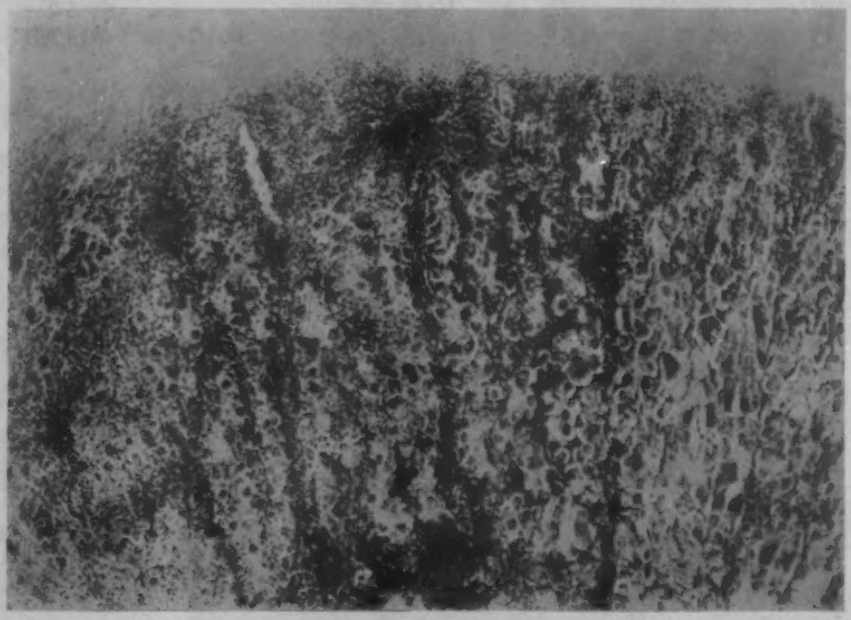

Fig. 8.—Photomicrograph of an area of intense hemorrhage taken from the stomach of dog 203 B, showing: (1) an area in the lower right corner uninvolved by hemorrhage, (2) the areas of hemorrhage in the middle and upper portions, spotted with islands of normal mucosal cells, and (3) the area on the left in which all cellular elements have disappeared. It is noteworthy that this area shows no evidence of crater formation.

The following protocols are representative:

Dog 2 A.—*Description.*—The dog, a small wire-haired male terrier, was in excellent physical condition. It had been in the cage under observation for five days, had passed normal formed feces and had an excellent appetite.

Operation.—On April 14, 1932, the hypothalamus was exposed with good visibility. A bent needle was projected into the brain tissue at what was judged to be the middle of the anterior part of the hypothalamus; it was then pressed

15. Keller, A. D.; Hare, W. K., and D'Amour, M. C.: Proc. Soc. Exper. Biol. & Med. **30**:772, 1933.

ventrally against the bone and again dorsally. No surface bleeding was elicited. The usual closure was made.

Postoperative Observations.—April 14, 7:30 p.m.: The dog was lying on its side, groaning loudly and executing violent running movements. The rectal temperature was 43 C. (109.4 F.). The dog was placed immediately in cold water, which quieted it.

10:30 p. m.: The dog was still quiet and had a normal rectal temperature of 39 C. (102.2 F.).

April 15, 8:30 a. m.: The dog walked about the room with a staggering gait. When picked up it vomited (analysis of the vomitus showed no free acid, 50 degrees of combined acid and no bile). Immediately after vomiting the dog was given 25 cc. of water by stomach tube, which it vomited immediately. In this vomitus were one large clot and several small clots of fresh (arterial) blood.

5 p. m.: The dog was given a piece of meat, which it vomited immediately, suspended in dark bloody fluid (the analysis of the vomitus revealed no free acid and 100 degrees of combined acid).

7 p. m.: The dog was given another piece of meat, which it immediately vomited, suspended in thin, slimy coffee-ground-colored vomitus. (This vomitus differed from the previous specimens in containing mucus). The rectal temperature was 36 C. (96.8 F.).

April 16, 9 a. m.: The temperature was 37.2 C. (98.9 F.). The dog appeared well but slept continually unless disturbed.

Autopsy.—The dog was found dead some time after lunch on April 16. The stomach contained a considerable quantity of blood. The mucosa of the stomach was unbroken but was involved by pronounced arterial hyperemia.

Dog 8 A.—*Description.*—A small black dog had been in a cage under observation for the past week. The feces had been formed.

Operation.—On May 3, 1932, the hypothalamus was exposed, and an extensive transverse cut was made with a bent probe just anterior to the internal carotid artery. Little bleeding resulted, and the usual closure was made.

Postoperative Observations.—May 3, 10 p. m.: The temperature was 32 C. (89.6 F.). The dog was inactive but stretched its legs when the temperature was taken.

May 4, 8 a. m.: The temperature was 30 C. (86 F.). There was no shivering. The respiratory rate was 100 per minute. The dog had passed thick mucus which was stained with fresh blood. The feces at first were thought to consist of undigested chopped meat, but on careful examination they were found to be composed of thick red mucus. The dog passed more of this material after the temperature was taken.

One hundred cubic centimeters of milk was fed by stomach tube. Vomiting began before all the milk was taken. The vomitus consisted of coffee-ground-colored liquid.

2 p. m.: The dog at this time was gasping.

Autopsy.—The gastro-intestinal tract was removed immediately after death. The stomach contained a considerable amount of the coffee-ground-colored fluid, in which were suspended many small black blood clots. The mucosa was unbroken, but it showed striking hyperemia.

Dog 27 A.—*Description.*—The dog was a shaggy yellow female, weighing 5.9 Kg.

Operation.—On Nov. 29, 1932, at 4:15 p. m., the base of the brain was exposed by the subtemporal approach. A bilateral transverse lesion in the anterior part of the chiasm was attempted by injecting a bent probe into the brain tissue just above and anterior to the internal carotid artery. The operative field was dry throughout the procedure.

Postoperative Observations.—November 29, 9 p. m.: The dog was coming out of the anesthesia and was vocalizing. Soft, partly formed, whitish-yellow feces were passed.

November 30, 9 a. m.: The dog got on its feet and vocalized periodically. It lay in the cage at rest between the periods of activity. The rectal temperature was 35 C. (95 F.). There was no shivering.

When the animal was picked up, semiliquid and soft, whitish-yellow feces fell from the rectum; directly after this more feces were passed, of the same character except that they were stained with arterial blood.

11 a. m.: More feces were passed at this time, consisting mostly of thick mucus colored with arterial blood. The animal was fed two large pieces of meat by placing them in the back of the mouth. It did not vomit and snapped at the hand and growled when fed. There was periodic activity.

5:20 p. m.: The dog was heard vocalizing from an adjoining room.

5:30 p. m.: The dog was found dead. It was still warm and limp. The floor of the cage and the hair about the rectum were covered with dark blood.

Autopsy.—The thorax and lungs were of normal appearance.

The abdomen was normal except that the omentum appeared somewhat reddened. The stomach and small bowel showed no abnormalities of the serosal surfaces. The large bowel was markedly constricted and appeared red, owing to engorgement of the surface vessels. The pancreas was markedly hyperemic. The rest of the abdominal organs appeared normal.

The lumen of the stomach contained two pieces of undigested meat and free blood. The body of the stomach and the pylorus were markedly red and spotted with small attached blood clots (fig. 5). The fundus was blanched. The proximal portion of the duodenum was blanched for a short distance, and then it also became markedly reddened, with blood and mucus in the lumen. The whole of the small bowel tended to be hyperemic, and there was a considerable amount of free unclotted blood and thick mucus in the lumen. The mucosa of the large bowel was thrown into longitudinal folds, the crests of which were hemorrhagic.

The surface of the brain was clean, the pia being unbroken along the base. The location and extent of the lesion are indicated in the photographs shown in figure 3.

Dog 85 B.—*Description.*—The dog was a light brown female, weighing 8.2 Kg.

Operation.—On March 28, 1933, at 3 p. m., a bilateral transverse lesion was made at the level of the chiasm.

8 p. m.: The rectal temperature was 34 C. (93.2 F.). The dog was shivering. No feces were passed.

March 29, 7:45 a. m.: The dog was found dead by an attendant.

9 a. m.: The dog was in rigor, but the abdominal viscera were still warm. A small amount of normal feces had been passed, followed by a considerable quantity of thick, clear mucus.

Autopsy.—The thorax was normal.

The omentum was distinctly reddened. The pancreas was pink, and the mesenteric lymph nodes were red and swollen, particularly those about the ileocecal junction.

When the esophagus was severed from the stomach, a considerable quantity of bloody fluid escaped from the stomach. The mucosa of the body of the stomach exhibited multiple small as well as large delimited hyperemic areas and attached blood clots (fig. 6 *A*).

The lumen of the duodenum contained clear, thick mucus. The mucosa displayed distinct early generalized arterial hyperemia. In the jejunum fluid was again encountered, whereas in the ileum there was clear, thick mucus. The large bowel appeared normal.

Removal of the Brain: There was blood in the temporal fossa, but the base of the brain was clear. The lesion had completely sectioned the optic tracts bilaterally just as they emerged from the chiasm caudally.

Observations on the Brain After Hardening: The lesion was fairly clean. It sectioned the hypothalamus back of the chiasm ventrally and slanted in a cephalic direction in passing dorsally. There was no free blood in the dorsal or the ventral portion of the third ventricle, but a small clot was present in the anterior horn of the left lateral ventricle. The hypophysis was uninjured. Certainly, the whole of Beattie's "anterior hypothalamus" was eliminated by this lesion, whereas his so-called "posterior hypothalamus" was grossly intact.

Of the 20 dogs in which the hemorrhagic states were precipitated, 12 died in twenty-four hours or less, 4 died in less than forty-eight hours and the remaining 4 died within seventy-two hours after operation. In a few instances hyperemia with traces of bleeding into the lumen was evident at death from eight to twelve hours after placing the central lesion (fig. 6 and protocol for dog 85 A).

In 19 dogs hemorrhage of the gastro-intestinal tract followed a lesion in the hypothalamic region, and in the remaining instance, a transverse section at the middle level of the midbrain, which lacked only a millimeter or so medially of a hemisection. In 14 the hypothalamic lesion passed bilaterally in a transverse direction through the anterior portion of the hypothalamus, i. e., at the level of the optic chiasm; in these dogs the caudal extent of the lesion varied from the cephalic tip of the chiasm (dog 27 A, fig. 3) to the caudal tip. In 3 instances the lesion was placed well back of the anterior portion of the hypothalamus, encroaching on the tuberal nuclei and leaving the posterior portion of the hypothalamus intact (protocol for dog 85 A). In 1 dog the lesion was placed longitudinally, separating the lateral and medial hypothalamic nuclei on one side. In the remaining animals the precipitating lesion was a slanting hemisection of the brain stem so placed as to cut ventrally cephalad to the optic chiasm and dorsally just caudal to the thalamus.

In analysis it is important to point out that in 18 of the 20 dogs the lesion reached the third ventricle, so that the ventricular fluid had direct communication with the débris of the lesion. In certain of these animals blood entered the ventricle, as evidenced by the presence of clotted blood (fig. 3). However, typical mucosal changes occurred after well delimited lesions with no evidence of blood actually present in the ventricles. Two of the lesions did not extend to the ventricle, namely, the transverse cut

through the midbrain and the lateral longitudinal lesions through the hypothalamus. Of particular importance is the fact that typical hemorrhagic states, previously described, were induced after lesions which had completely destroyed the anterior portion of the hypothalamus and encroached on the tuberal region. In no instance was there evidence of increased intracranial pressure, as would be indicated by intracranial hemorrhage or edema of the brain.

Crater Formation in the Gastric and Duodenal Mucosa.—Characteristic crater formation in the mucosa of the body of the stomach was also encountered. The craters were small in diameter, though penetrating, and as a rule they were situated on the crests of the mucosal folds (figs. 9 *A* and *B*). They were located throughout the body of the stomach but were more numerous in the distal portion, i. e., the region adjacent to the pylorus. In two or three instances, in addition to craters in the mucosa of the body there were several small shallow erosions in the pylorus as well as on the pyloric sphincter and in the proximal portion of the duodenum. These craters were not associated with hyperemia of the mucosa. In 1 instance (dog 84 B) large penetrating twin duodenal ulcers were present unassociated with gastric pathologic lesions (fig. 10). Protocols for dogs 29 B, 164 B and 447 B are typical for animals with gastric involvement, while the protocol for dog 84 B is included because this animal was the only one in the series having twin duodenal ulcers.

Dog 29 B.—*Description.*—The dog was a wire-haired male, weighing 5.4 Kg.

Operation.—On Dec. 5, 1932, a bilateral section was made with a bent probe just anterior to the chiasm.

Postoperative Observations.—December 6 (first day), 9 a. m.: The temperature was 32 C. (89.6 F.). The dog was shivering and whining. It had passed dark formed feces and had vomited.

9 p. m.: The temperature was 35 C. (95 F.). The dog was normally alert but fought hard the drawing of blood. No more feces were passed.

December 7 (second day), 9 a. m.: The temperature was 39.2 C. (102.6 F.). The dog was up and alert and appeared normal. No feces were passed.

December 8 (third day), 7 a. m.: The dog was found dead, but it was still warm.

Autopsy.—The stomach was empty. The mucosa was blanched, and the mucosa of the body contained multiple small penetrating ulcers; these were more numerous in the region just adjacent to the pylorus. There was no evidence of change in the pylorus or the duodenum.

The brain after removal displayed a massive bilateral lesion passing through the anterior tip of the optic chiasm. There were a blood clot in the anterior horn of the right lateral ventricle and a thin leaf of clot in the ventral tip of the third ventricle. The rest of the ventricular system was clean.

Dog 164 B.—*Description.*—The dog was a shaggy female, weighing 5.8 Kg.

Operation.—On Nov. 20, 1933, a transverse chiasmal lesion was placed with a bent needle. Good exposure and closure were effected.

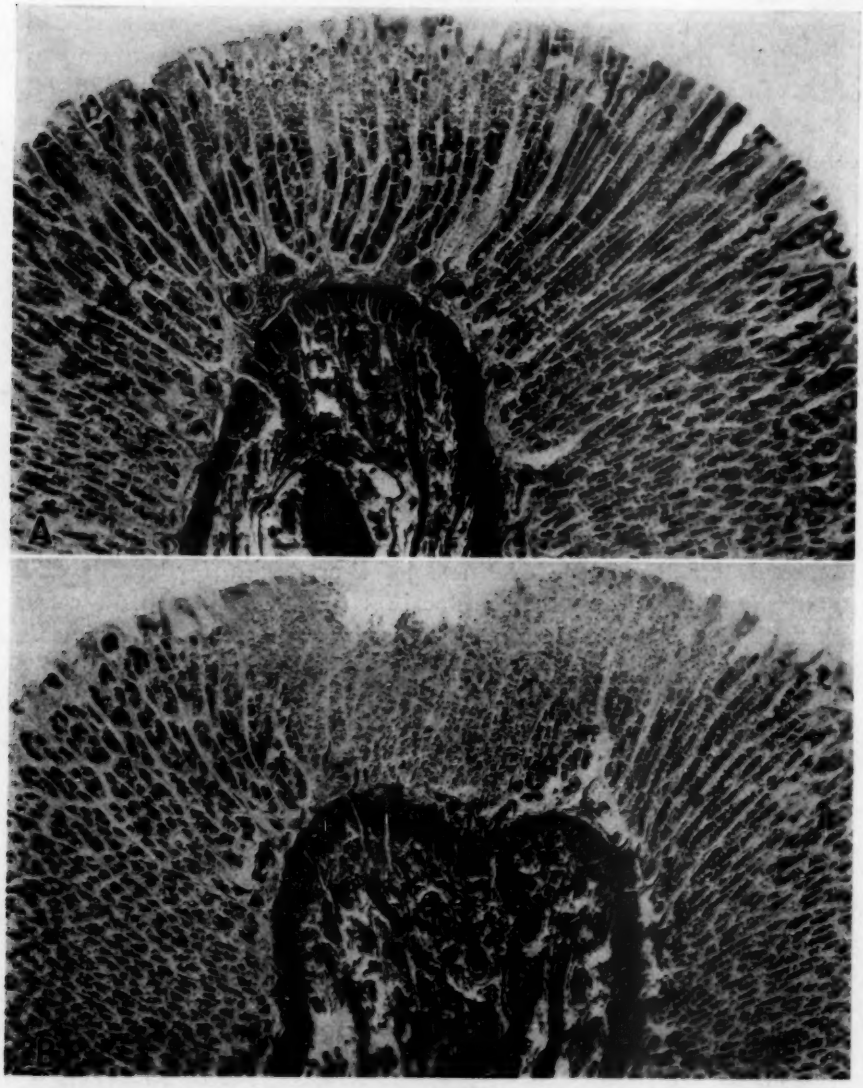

Fig. 9 (dog. 29 B).—*A* is a photomicrograph of a mucosal fold of the stomach, showing on the crest the precursor of a crater. This particular area is shown at its greatest depth. *B* shows another fold of the same stomach from which the section appearing in *A* was taken. The following conditions can be seen: (1) the beginning of crater formation; (2) the acidophilic cells, which with this magnification stand out clearly, and the disappearance of the basophilic cells; (3) the heavier staining of the basophils immediately surrounding the area, and (4) the indenting of the muscularis.

Postoperative Observations.—November 21 (first day), 8 a. m.: The temperature was 37.8 C. (100.1 F.). The dog was out of the anesthesia but was quiet.

8 p. m.: The temperature was 38.5 C. (101.3 F.). The dog was sleeping in the cage.

November 22 (second day), 7 a. m.: The dog was found dead.

Autopsy.—The lumen of the stomach contained blood, but the mucosa was not hyperemic. There were multiple small craters on the crest of the mucosal folds of the distal portion of the body of the stomach.

The brain displayed a bilateral transverse lesion just at the anterior tip of the chiasm. There were a blood clot in the right lateral ventricle and possibly a small

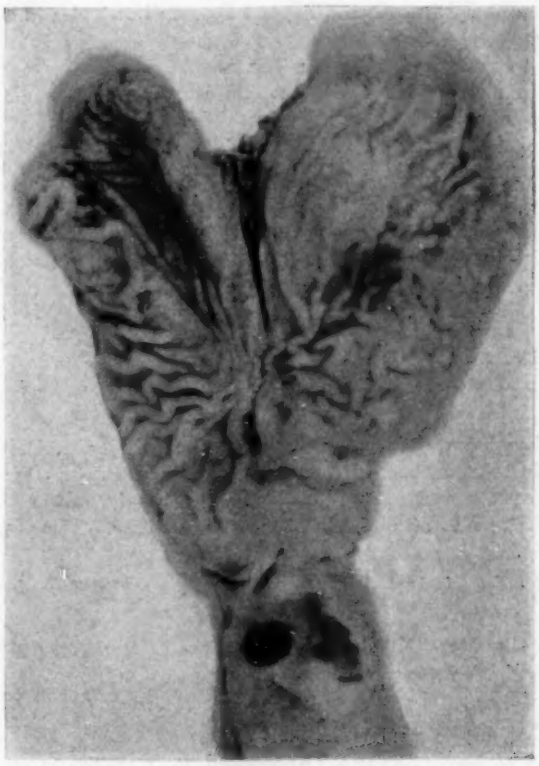

Fig. 10.—Photograph of the stomach of dog 84 B, showing the prominent twin ulcers of the duodenum. The round lesion on the left had perforated the coats of the wall except the peritoneum.

clot in the ventral part of the third ventricle. The rest of the ventricular system was free from blood.

Dog 447 B.—*Description.*—The dog was a black wire-haired female, weighing 6 Kg.

Operation.—On Oct. 24, 1934, the superior colliculus was exposed by elevating the occipital pole. Since the tentorium was short, leaving the anterior part of the cerebellum exposed, an attempt was made to expose the brachium conjunctivum by

breaking the pia and separating the inferior colliculus from the cerebellum by use of gentle traction on the inferior colliculus. The needle was then passed into the lateral portion of the stem in an attempt to destroy only the brachium conjunctivum. I believe the lesion was too extensive. Excellent exposure was made; there was no bleeding, and the cerebellum was not compressed.

Postoperative Observations.—October 24, 4:30 p. m.: The temperature was 40 C. (104 F.). There was no shivering.

October 26 (second day), morning: The temperature was 38.2 C. (100.8 F.). The left limbs were definitely "out," and there was absence of correcting and placing ability. The dog drank milk and ate salmon readily.

October 30 (sixth day), morning: The dog was in excellent physical condition and in good spirits. It had a good appetite but had vomited once on the preceding day.

November 2 (ninth day), 11 a. m.: The dog drank milk vigorously and vomited it about fifteen minutes later. The mouth was marked by ulcers, and blood dripped from the mouth into the milk on drinking.

November 3 (tenth day), 9:30 a. m.: The dog appeared ill and was weak. It drank milk but vomited it.

10 a. m.: The dog was gasping.

Autopsy.—The walls of the stomach were relaxed but not dilated. The mucosa was coated with mucus, with a few small black blood clots in suspension. There was no fluid in the lumen. The mucosa of the body was involved by multiple craters on the crests of the folds. The intact mucosa was free from any well delimited areas of hyperemia or hemorrhage, although it was somewhat red in places. The pylorus and duodenum were normal.

The brain was well injected, and all the surfaces were clean. There was a free communication between the fourth ventricle and the subdural space where the pia had been broken between the cerebellum and the inferior colliculus. The lesion involved the dorsolateral part of the pons, encroaching rather close to the level of the entrance of the cerebellar peduncles. The inferior colliculus was slightly macerated. There was no blood in the fourth ventricle. The path of the lesion contained fibrin.

Dog 84 B.—*Description.*—The dog was a shaggy yellow female, weighing 5.7 Kg.

Operation.—On March 28, 1933, at 2:30 p. m., a transverse bilateral chiasmal lesion was placed with a bent needle.

Postoperative Observations.—March 28, 8 p. m.: The temperature was 40.8 C. (105.4 F.). The dog was shivering.

March 29 (first day), 8 a. m.: The temperature was 40 C. (104 F.). The dog was in good condition. It walked about the room and sat on its haunches. It drank milk readily.

March 30 (second day), 8:30 a. m.: The temperature was 38.2 C. (100.8 F.). The dog was shivering. The appearance was normal in every respect. The animal passed formed feces and drank milk readily.

April 2 (fifth day), morning: The temperature was 39 C. (102.2 F.). It was noticeable that the dog was shivering, particularly since the other dogs in the same room were not. The animal seemed slightly depressed.

April 8 (eleventh day), 8 a. m.: The temperature was 38.9 C. (102 F.). Shivering was constant. The dog ate normally and passed formed feces.

10:30 a. m.: The temperature was 39.5 C. (103.1 F.). The dog was placed in the icebox at 45 F.

6:30 p. m.: The temperature was 39 C. (102 F.). The dog was shivering. It was left in the icebox overnight.

April 9 (twelfth day), 8 a. m.: The temperature was 39 C. (102 F.).

10:30 a. m.: The temperature was 39 C. (102 F.). The dog was taken out of the icebox and placed outdoors in the yard.

June 3 (sixty-seventh day), morning: The dog was found dead in rigor. It had been maintained since the twelfth day after operation in an outdoor yard without special care.

Autopsy.—The abdominal cavity was clean. The liver was pale, almost white, and soft (fig. 11). The gallbladder was practically empty, containing only about 1 cc. of fluid, which was almost colorless. The stomach was dilated and contained

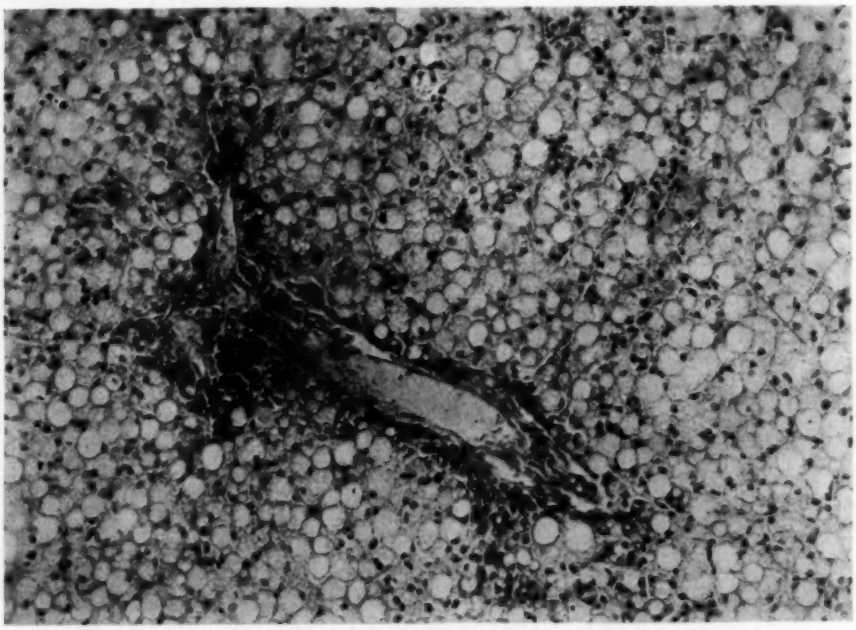

Fig. 11 (dog 84 B).—Photomicrograph of a section of the liver. A description by Dr. Kistler is given in the protocol.

a great deal of hair and black blood. The mucosa of the stomach was blanched and intact except that a small crater was present in the pylorus near the pyloric sphincter. The lumens of the small and large bowels were filled with black blood. The mucosa was blanched and intact except that two large ulcers occurred in the most proximal portion of the duodenum (fig. 10). One of these had completely perforated the layers of the wall except the peritoneum. This ulcer was filled with blood and was undoubtedly the source of the blood which filled the stomach and intestine.

The surface of the brain was clean. As evidenced by a study of serial sections through the hypothalamic region, the lesion on the right side involved only the immediate ventral region adjacent to the chiasm. On the left side the whole area dorsal to the chiasm (anterior portion of the hypothalamus) extending dorsally

to the level of the anterior commissure was involved. All the hypothalamus caudal to the chiasm was intact, as was the hypophysis.

Dr. G. H. Kistler described the following histologic picture (fig. 11) of the liver:

In the histologic preparations of the liver stained by the Maximow method it is estimated that about 85 per cent of the tissue was occupied by large, medium-sized and small clear spaces, such as those which remain when fat is dissolved out. The remaining 15 per cent of the tissue in the sections examined was composed of hepatic triads surrounded by narrow margins of liver cells. These cells were compressed, and they stained poorly except those in close contact with the vessels of the triads. Near the centers of the lobules about the remaining liver cells were a few scattered small round cells which were assumed to be pyknotic nuclei of liver cells now replaced by fat. Supporting the fat globules was a fine fibrillar stroma which in places seemed to have a minute meshwork with a pale pink-staining reaction, such as is observed in edema. There was a small amount of blood in the poorly defined central veins and no perforation of the bile ducts.

The large amount of fat present in these tissues was decidedly out of proportion to the amount of hyperemia and other changes that usually precede fatty changes, and for that reason the morphologic structures were not compatible with the usual conception of such changes in the liver. It is also noteworthy that the small amount of liver tissue remaining was present in close contact with the vessels of the hepatic triads.

Histologically, the precursor of the crater consisted of a funnel-shaped area in which there was complete absence of the basophilic cells and in which the acidophilic cells were much more sharply defined than those not present in the involved area. In instances of less involvement the change was confined to the surface of the mucosa (fig. 9 *A*), while in more advanced stages the centers of the lesions penetrated to the muscularis (fig. 9 *B*). The material from the central portion of the area apparently sloughed, forming the crater, the actual defect appearing grossly as whitish tissue both about the border and in the depth of the crater. Immediately surrounding the involved area the basophilic cells stained more deeply than those situated more distally; otherwise, the intact cells appeared essentially normal (fig. 9 *B*). The mucosa showed no evidence of blood, although the submucosal vessels were engorged as a rule. Serial sections demonstrated that the white plugs described in the preliminary report [15] never produce actual occlusion. That these nonoccluding clots are not the cause of the craters is evidenced by the fact that craters occur in the complete absence of these clots. Further, we have since been able to duplicate the white clots in the gastric and hepatic vessels by maintaining animals on which no operation had been performed for several hours under deep pentobarbital sodium anesthesia without any indication of gastric pathologic changes. Accordingly, we believe that the clots are due, in part at least, to the slowing of circulation resulting from "slow death" and that they do not contribute to the formation of the gastric craters.

Definite multiple gastric craters were induced in a total of 11 dogs. Eight of these animals were dogs having transverse chiasmal lesions, all

of which involved only the cephalic part of the anterior portion of the hypothalamus, thus leaving the major portion of this region intact. Nine of the dogs died approximately forty-eight hours after operation; 1 died on the fifteenth day, and the remaining 2 had small healing craters when the experiments were terminated, on the twenty-sixth day, a few days after the markedly ulcerated mouths had begun to heal. The remaining 3 dogs in which gastric craters occurred had pontile lesions. In all 3 instances the craters were discovered several days after operation (protocol for dog 447).

In analysis it should be pointed out that the number of instances of craters produced after lesions of the anterior part of the hypothalamus was much greater than that after pontile lesions and that in animals with lesions of the midbrain, medulla and cerebellum no craters were observed. Also of possible significance is the fact that craters were not noted as early after operation as were the hemorrhagic states. It should also be stressed that in no instance has there been any sign of a non-healing defect.

Gastro-Intestinal Changes Occurring Apparently as a Result of Stimulation by Way of the Ventricular System Rather Than by Localized Traumatic Injury.—The frequent occurrence of bleeding into the ventricles of the brain as a result of placing hypothalamic lesions forced us at the outset to recognize the possibility of stimulation by way of the ventricular fluid as a major complicating factor in localization studies in which traumatic lesions were utilized. Although we have not yet begun a systematic comprehensive investigation of this phase of the problem, we have several distinctive protocols, which are reported here as they clearly indicate that the aforementioned stimulation occurs.

1. Precipitation of Gastric Erosions by the Intraventricular Injection of Blood: That blood in the ventricles can precipitate gastric pathologic changes is evident from the protocol for dog 33 B:

Dog 33 B.—*Description.*—The dog was a reddish-brown shaggy female, weighing 5.2 Kg.

Operation.—On Dec. 15, 1932, at 2:30 p. m., a small amount of whole untreated blood was drawn from a vein of the leg of the dog and was introduced into the third ventricle by passing the needle through the exposed corpus callosum. No blood escaped around the needle. There was no evidence of increased tension of the brain at any time after the injection or during the closure.

Postoperative Observations.—December 15, 9 p. m.: The temperature was 35 C. (95 F.), and the dog was shivering. It vocalized loudly when the thermometer was inserted.

December 16 (first day), 9 a. m.: The temperature was 36 C. (95 F.). The room temperature was 60 F. The dog was up and about and was shivering markedly.

Dec. 17 (second day), 10 a. m.: The temperature was 31 C. (87.8 F.). The room temperature was 70 F. The dog was shivering markedly. When placed on the floor it walked about with a staggering gait, nosing the floor as though hungry. Milk was offered, which it refused. The animal was then placed in the incubator.

5:30 p. m.: The dog was dead.

Autopsy.—The abdominal cavity was clean, and the stomach and small bowel were in tonic contraction. The stomach was empty except that thick mucus coated the mucosa. The crests of the folds of the body of the stomach adjacent to the pylorus were involved by multiple well delimited craters. There were also two rather large craters in the pylorus. The intact mucosa of the stomach was blanched. The duodenum showed no involvement except slight arterial hyperemia. There was no blood in the lumen.

The brain was relaxed and clean on all its surfaces. After it had been hardened in formaldehyde, sectioning revealed a thin blood clot in the anterior horns of the lateral ventricles, in the dorsal and ventral portions of the third ventricle and in the middle of the fourth ventricle. The blood clot was distributed as a thin sheet through the third ventricle. There was no evidence of dilatation of the ventricles as a result of the presence of blood.

In this instance there was no injury to any part of the brain other than that at the site of injection through the corpus callosum, the blood being distributed through the ventricles as a thin leaf in such a manner that the ventricles were not dilated, and, in our opinion, the movement of the cerebrospinal fluid was not impeded. Such a striking result cannot be dismissed as without significance, although in other instances greater and less amounts of blood in the ventricles have failed to precipitate gross changes in the gastro-intestinal canal. It may be noted that the postoperative course and the lesions of the gastro-intestinal tract exactly paralleled those of dog 29, which had a chiasmal lesion.

2. Bleeding into the Lumen of the Stomach Resulting Seemingly from Blood in the Ventricles: A striking instance of bleeding into the lumen of the stomach from the mucosa of the body unassociated with hyperemia of the mucosa was encountered in dog 197 B. The right hook bundle and the brachium conjunctivum were successfully cut in December 1933. In February 1935 the anterior portion of the left cerebral hemisphere was removed with a view to studying the effect on the signs of cerebellar involvement of removal of the corresponding motor area. After the operation the dog exhibited great excitement and gave evidence of internal pain. On the sixth day the beginning of deterioration was suspected; therefore, in order to preserve better the chronically involved cerebellar tissue, the dog was killed.

The gastro-intestinal tract was normal except that a considerable amount of black clotted blood was mixed with the thick mucus covering the mucosa of the body and also occurred in the proximal portion of the duodenum. In figure 12 *A* is shown the unfixed specimen, and in figure 12 *B*, the same specimen after fixation in Klotz' fluid [15a] and removal of

15a. The formula for Klotz' fluid follows:

Solution 1.—Water, 10,000 c.c; chloral hydrate, 400 Gm.; sodium chloride, 90 Gm.; sodium bicarbonate, 50 Gm., and a solution of formaldehyde, 300 cc.

The specimen should remain in this solution from three to twenty-one days, according to the size and density of the tissue. It should then be briefly washed in running water and stored or mounted in solution 2.

Solution 2.—Water, 10,000 cc.; chloral hydrate, 200 Gm.; sodium chloride, 90 Gm.; sodium bicarbonate, 50 Gm., and phenol, 25 Gm.

the blood. The blood was limited to the body of the stomach (area of acid production), and the mucosa of this region was blanched.

The brain was relaxed, and the surface was free from blood. The space from which the brain tissue was removed contained blood. Careful examination after fixation revealed that the lateral and third ventricles communicated with the subarachnoid space through a small opening anteriorly at the level of the anterior commissure. The whole ventricular

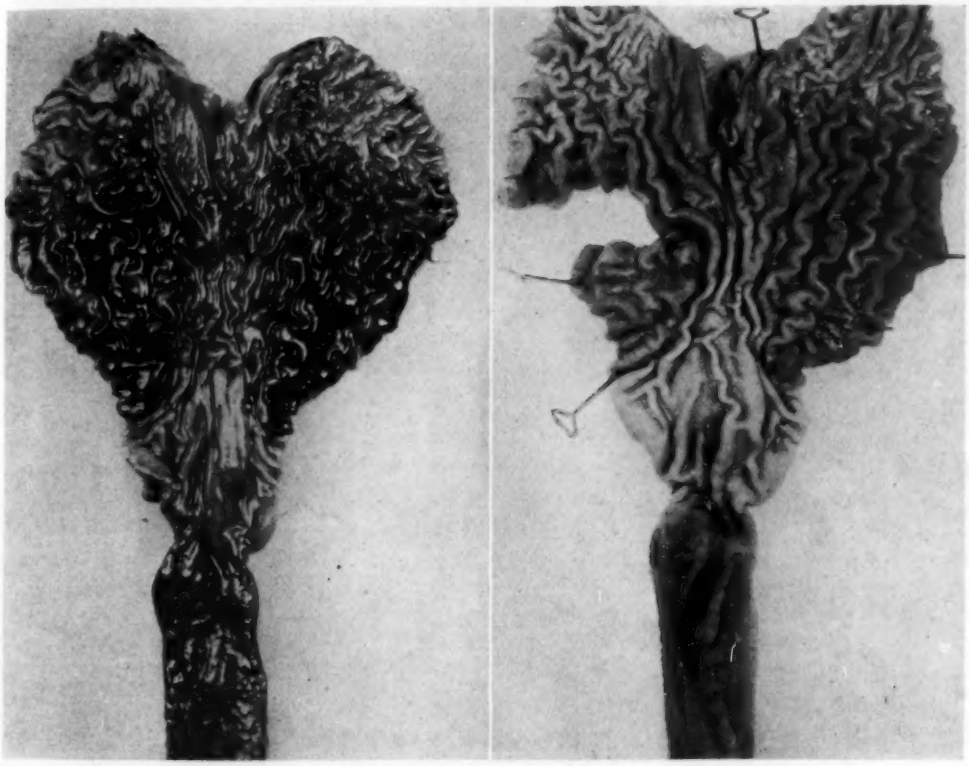

Fig. 12 (dog 197 B).—At the left is a photograph of the unfixed stomach and duodenum, showing blood confined to the body of the stomach and the duodenum, and at the right, a photograph of the same specimen after fixation in Klotz' fluid and removal of the blood and mucus. Although the fundus and pylorus are readily distinguishable from the body of the stomach, the body is not hyperemic.

system of the brain contained a thin leaf of blood clot. A variable factor other than blood in the ventricles that may enter into consideration in this instance is a possible disturbance in the normal direction of flow of the cerebrospinal fluid, such as might result from the new opening, if patent, between the ventricular and the subarachnoid system. I believe

that the removal of the frontal lobe was not a causative factor, since the opposite lobe remained intact. The possibility that a disturbance in the normal flow of the cerebrospinal fluid might be deleterious to an animal seems rather probable in that the incidence of deterioration is high in dogs after relatively clean unilateral removal of the anterior portion of the cerebral hemisphere, i. e., when there is slight if any hemorrhage into the ventricles. This is not true in instances of removal in which the ventricles are not opened anteriorly at the level of the anterior commissure, as when smaller portions of the anterior part of the hemisphere are removed or when a blood clot fills the vacant space. Further, extensive traumatic bilateral lesions involving the whole ventral portion of the anterior parts of the hemispheres did not impair the digestion or life of any of the six dogs. Massive lesions encroaching on the region of the anterior portion of the hypothalamus were, however, incompatible with life, and a high incidence of gastro-intestinal pathologic lesions likewise followed.

We also suspect, problematically, a disturbance in the cerebrospinal fluid in instances in which pathologic change follows lesions in the pons when the approach has been made dorsally by breaking the pia between the cerebellum and the inferior colliculi. Thus, in dog 447 the location and extent of the lesion as well as the absence of blood in the ventricles and in the path of the lesion fail to explain satisfactorily, in the light of the many lesions in this region, the changes in the digestive tract noted in this animal. The 3 monkeys in our series in which the pia was broken before the lesion was made died a few days after operation with hemorrhages of the gastro-intestinal canal, whereas the other monkeys, which had essentially identical lesions but in which the pia was not broken previous to placing the lesion, survived to "chronicity."

3. Progressive Inhibition of Gastric Digestion Following Certain Extensive Hypothalamic Lesions: Impaired digestion following severance of the hypothalamus in cats has been previously described.[15] The same condition has subsequently been encountered in dogs, it being further noted that in these instances the hyposecreting stomach also failed to empty, as evidenced by marked overfilling. The fact, which was early appreciated, that impaired digestion and emptying of the stomach were not present in all the animals in which the hypothalamus was removed, made us suspect that we were not dealing with a strict deprivation or release phenomenon, at least, certainly not to the extent, for example, to which one can associate heat regulation with the hypothalamus.[16] A possible and probable explanation of the aforementioned

16. Keller, A. D., and Hare, W. K.: Proc. Soc. Exper. Biol. & Med. **29**:1069, 1932. Keller, A. D.: Am. J. M. Sc. **185**:746, 1933; Am. J. Physiol. **113**:78, 1935.

disturbances is clearly suggested in the protocol for dog 541, in which the access of the cerebrospinal fluid to the necrotic débris of the lesion was the only variable. For the first several days following the coring of the caudal and dorsal connections of the hypothalamus, this dog maintained the following constant picture:

1. There was complete loss of ability to maintain the body temperature.

2. The dog exhibited adequate righting and tonic mechanisms in righting itself and walking without falling; however, it showed a complete lack of interest in the surroundings and exhibited spontaneous movements only prior to defecation or urination.

3. The dog exhibited typical cataplexy in allowing the legs to remain in awkward lateral positions and in characteristic sagging at the wrists. Yet, it was of interest that the dog always corrected the forefeet, although there was definite delayed correction in both hindfeet.

4. The dog did not usually object to being handled, but it exhibited typical rage, such as growling, when the temperature was taken or when slight stimulation was applied. When it was bathed it fought and growled severely during the whole process. The minuteness of stimulation necessary to induce rage was demonstrated when in walking one day about the floor the dog caught a rear leg over the round of a stool; it growled furiously for several minutes because of this slight resistance to its movement.

5. Normal gastric function was evidenced by the absence of regurgitation of food after feeding and by the passage of normal formed feces. In two instances in which the rectal temperature approached 37 C. (98.6 F.) spontaneous vomiting occurred. This vomiting disappeared when the temperature was lowered, as was true of other animals, to be described later.

The first deviation of the digestive tract from the normal condition was seen on the ninth day, when dripping of saliva was noted. Examination of the mouth revealed edematous mucous membranes. Ulceration of the mouth subsequently developed progressively, until at the time of death practically the whole mouth was involved by large penetrating ulcers. On the sixteenth day regurgitation of food occurred directly after feeding even though the rectal temperature was only 31 C. (87.8 F.). At the same time it was noted that the abdomen was distended, and it remained so. About this time the feces changed from the formed type to the semiliquid and liquid states; on one occasion the feces were noted to be clay-colored. The regurgitation of food became more severe on feeding and later occurred spontaneously.

The dog was fed for the last time on the seventeenth day after operation. Dextrose was administered subcutaneously on the eighteenth day. On the morning of the nineteenth day the dog was found dead. The stomach was markedly filled with undigested food (Purina Chow). The amount of food remaining in the stomach was surprising when one considers that the dog was not fed for from thirty-six to forty-eight hours prior to death and that a considerable amount of vomiting

occurred during the two or three days before death. The gastric contents did not contain blood; however, the mucosa of the proximal portion of the pylorus and the distal portion of the body of the stomach exhibited multiple pinpoint hemorrhages. There was no hyperemia elsewhere in the stomach. The duodenum was normal. In spite of the long sojourn of the food in the stomach, analysis of specimens of the semiliquid gastric contents revealed no free acid and barely a trace of combined acid.

The brain was removed successfully with the hypophysis attached. There was no blood on the surfaces except a small clot on one side of the path of the lesion. The temporal poles were intact on both sides. Serial sections of the thalamus stained for fibers revealed complete separation of the hypothalamus from its caudal and dorsal connections and dorsal softening involving the whole of the anterior two thirds of the thalamus. None of the hypothalamic tissue was softened. There was no blood in the ventricles or in the path of the lesion; however, the width of the path gave evidence that a leaf of blood clot had been present. The necrotic tissue of the thalamic softening was in direct communication with the cerebrospinal fluid and had been "thinned" by it. Dogs and cats tolerate well large softenings of the thalamus to the point of complete organization in instances in which the third ventricle is not encroached on.

Ulceration of the Mucous Membranes of the Mouth Following Lesions of the Brain Stem.—Early in the series of experiments,[17] marked ulceration of the mouth was encountered several days after operation in dogs having lesions in the chiasmal region which were not extensive enough to cause the early death of the animals. The study of the process revealed that a few days after operation the gums and mucous membrane of the mouth became reddened. The hyperemia progressed in a few days to localized bleeding points at various sites, particularly on the cheeks and the upper lip. The bleeding points developed into penetrating ulcers, which continued to enlarge in all directions until the death of the animal or until the process was abruptly reversed and healing occurred rapidly. At the height of the process in instances of severe involvement the mouth was largely an ulcerated mass, the face being constantly wet with bloody saliva. When the dog drank the milk was colored with blood dripping from the mouth. In mild lesions only a few shallow erosions formed, which healed soon after their appearance. Typical instances are described in the protocols for dogs 447 and 541. In a few instances in which the experiments were terminated when the process was at its height, a few localized black blood clots were suspended in the mucus coating the mucosa of the body of the

17. Keller, A. D.; Hare, W. K., and D'Amour, M. C.: Am. J. Physiol. **105**:61, 1933.

stomach. The mucosa under the clots showed no evidence of hyperemia or localized blanching. In two dogs there was evidence of a few very small, practically healed craters. In dog 447 only were typical gastric craters encountered.

Although we occasionally observed ulcers of the mouth in the stock dogs, they occurred only in animals in poor condition. It is certain that the process observed in the dogs in our series was precipitated by the intracranial procedure, because of the characteristic onset after operation (in from three to ten days) and the abrupt healing. Also, the process could not have been one of nutrition, since the dogs ate well during the seizure and the mouth likewise healed rapidly under the same cage regimen. Prolonged starvation of dogs for as long as three weeks did not precipitate changes in the mouth.

The question of the central mechanisms concerned is, of course, of interest. We greatly suspect that it consisted of stimulation via the cerebrospinal fluid, since the process so nearly paralleled what we judge to be the time of organization of the débris in the lesion. This theory is further supported by the fact that ulceration of the mouth has occurred after all types of lesions of the upper part of the brain stem which encroach on the ventricular system. In instances of massive subarachnoid hemorrhage about the base of the brain or about the cerebral hemisphere in which the ventricular system was intact ulceration of the mouth did not develop.

Gastric Changes Precipitated by Overheating Nonheat-Regulating Preparations.—Hyperemia of the mucosa of the body of the stomach with bleeding into the lumen was observed early in certain cats with the hypothalamus cored free from the brain stem. Crater formation was likewise encountered in a few cats with lesions in the midbrain, as has been previously reported.[15] Overheating was suspected as an etiologic factor, since we frequently noted that heating these preparations elicited vomiting whereas prior to the test the animals retained and digested food without outward signs of disturbance. All the preparations which showed gastric changes had a history of having been overheated.

The most striking instance of crater formation is that of cat 10. On Oct. 11, 1932, the brain stem was severed completely at the cephalic level of the midbrain. After operation the cat was at first fed by stomach tube, but later it ate readily when food was placed in contact with the nose. The digestion was normal, as evidenced by the absence of vomiting and by the passing of normal feces. On the ninth day after operation the rectal temperature was raised by heating the cat to 42.8 C. (109.1 F.), at which time it began to pant in a typical manner. The heating precipitated the passing of thick mucus by rectum, but no other outward disturbance in digestion was noted. The course did not change

from that just indicated until the forty-fifth day after operation, when the cat was again tested for panting. During the test the animal was forgotten, and when discovered it was panting typically and the rectal temperature was 43.8 C. (110.8 F.). The cat at this time was definitely prostrated with heat. Two hours later milk was given by stomach tube and was vomited almost immediately. The heating also precipitated the passing of a considerable amount of thick mucus by rectum. A few hours later the cat vomited spontaneously brown semiliquid material. The following day it was found dead in rigor.

The stomach was empty, and the mucosa of the body of the stomach was involved by three large erosions, the largest of which was bordered by several punched-out ulcers. About one half of the mucosa of the body was involved by these craters. The pylorus showed no actual craters; however, there were definite delimited whitish-gray areas in which the necrotic material had not yet sloughed. The small bowel was normal.

It would seem that the massive gross changes in the stomach were precipitated by the overheating, since the cat ate and digested food well during the acute stage following the transection. In the chronic stage the overheating was the only variable.

In dog 467 the hypothalamus was cored free from its connections, and the tissue was macerated subsequently with forceps. The first three days after operation the dog was fed by stomach tube and showed no evidence of vomiting. Normal formed feces were passed. In testing for panting on the third day, the rectal temperature was raised to 43.1 C. (109.6 F.), at which time vomiting began. Three hours later when fed by stomach tube the dog vomited the whole meal. It failed to retain food subsequently until the time of death, six days later. The day following the heating semiliquid feces with a considerable amount of mucus were passed. At death the body and fundus of the stomach exhibited characteristic generalized hemorrhagic necrosis (fig. 13). The pylorus was markedly edematous, whereas the duodenum was normal.

In this case again the gastric disturbance made its appearance definitely at the time of heating. It would seem probable that the heating precipitated the hemorrhage of the mucosa, which during the subsequent six days was modified to the characteristic picture of necrosis observed at death. The fact, however, that the animal lived for six days after the heating would make it possible for the pathologic changes to have been precipitated as a result not of the overheating but of ventricular stimulation resulting from the operative débris gaining access to the cerebrospinal fluid. In this instance probably both factors were involved.

That hyperemia of the gastric mucosa with bleeding into the lumen of the stomach can be precipitated by overheating a nonheat-regulating

animal is demonstrated in the instance of dog 476. In the case of this dog overheating was clearly the only variable, as the lesion was clean at the outset, and since the animal lived to the chronic state there was essentially no operative débris to complicate the picture. Operation was performed on the dog on Nov. 30, 1934, the caudal and dorsal connections of the hypothalamus being cored. After operation the animal was at first fed by stomach tube, but it later ate spontaneously, exhibiting an

Fig. 13 (dog. 467).—Photograph of the stomach, showing involvement of the entire body of the stomach by hemorrhage and necrosis and edema of the pylorus.

enhanced appetite, and it passed normal formed feces. There was no evidence of vomiting. On the eighteenth day after operation the rectal temperature was raised to 41.9 C. (107.4 F.), at which time typical panting occurred. During the heating a considerable amount of formed feces was passed. The following day the feces were unformed and semiliquid. No evidence of vomiting was shown. On two or three subsequent occasions the temperature reached from 39 to 40 C. (102 to 104 F.), the feces changing each time from the formed to the unformed

state. On the thirty-seventh day the dog was again heated until panting was elicited; the rectal temperature reached 42.6 C. (108.7 F.), and vomiting occurred. The following day semiliquid feces were passed which contained undigested milk curd. The dog died the second day after this heating. The lumen of the stomach contained approximately 100 cc. of bloody fluid. The mucosa of the body of the stomach was involved with marked generalized hyperemia. The duodenum and upper portion of the small bowel were also hyperemic and edematous. Analysis of the gastric contents showed no free acid and 64 degrees of total acid.

The extreme sensitivity of the gastro-intestinal mechanism of some of these preparations to increased heat is evidenced in the protocol for dog 541 already given. That the dog's former normal temperature of from 38 to 39 C. (100.4 to 102.2 F.) was deleterious after operation is shown by the fact that a rectal temperature of 37 C. (98.6 F.) invariably precipitated vomiting.

On the basis of evidence in the aforementioned protocols, there is no doubt that the elimination of the central (hypothalamic) heat-regulating mechanism releases gastric processes from the protective mechanism which is normally called into play during overheating. The reason that different preparations respond with different rectal temperatures is not known. The rate and duration of heating and the height of the temperature reached, the length of life after heating, the amount of operative débris and the extent of damage to the central mechanisms concerned are all variables which must be investigated carefully.

It is also now recognized that in the past the rapid deterioration of the nonheat-regulating preparations in our series has to a large degree been the result of the care in maintaining the temperatures of the animals at approximately the preoperative level. Processes other than those of digestion are concerned, since the maintenance of such a preparation at a high temperature level may produce deterioration without precipitating gross gastric pathologic changes. We can, accordingly, now predict the successful maintenance of these preparations for longer periods after operation by keeping the temperatures at from 32 to 35 C. (89.6 to 95 F.) rather than at from 37 to 39 C. (98.6 to 102 F.).

COMMENT

As Cushing [1] has pointed out, the association of gastro-intestinal pathologic changes and injuries of the central nervous system has in recent years been not only largely forgotten but even questioned. One can, I think, appreciate such skepticism in the light of the lack of uniformity in methods of approach and the results obtained by the earlier investigators. Evaluation of the worth of one investigation in relation to that of another is difficult if not impossible. The recent experimental

work of Burdenko and Mogilnitzki on dogs, Cushing's clinical operative experiences and the experiments of Watts, Fulton, Hoff and Sheehan on monkeys, however, leave no doubt as to the ability of intracranial procedures to precipitate acute antemortem pathologic changes of the gastro-intestinal tract. It is nevertheless evident that the matter is still vague in that little is known, as far as direct demonstration is concerned, of the mechanism whereby the pathologic change is produced.

When the question of mechanism is considered in relation to the aforementioned results, disturbance in the cerebrospinal fluid was clearly, in several instances, a major central factor that cannot be ignored. Such instances as those of dogs 33 B, 197 B and 541 are striking. The implications are far reaching, particularly in regard to clinical treatment during the acute stage following intracranial operations and accidents as well as in experimental work in which it is desired to maintain preparations to "chronicity" after lesions involving the cephalic portion of the ventricular system. It is obvious that in instances of increased concentration of the cerebrospinal fluid, if the stimulating factor is assumed to be ionic or osmotic, "forced perivascular drainage" as performed by the recently described method of Retan [18] would be highly beneficial if not crucial. Such a procedure would be indicated at any sign of gastro-intestinal disturbance or involvement of the mouth. The susceptibility of cells of the autonomic nervous system to drugs injected into the ventricles has been unmistakably demonstrated by Cushing,[7] Light [19] and Ferguson.[20]

The fact that, aside from purely ventricular involvement, pathologic lesions occurred spontaneously only after hypothalamic and pontile lesions may indicate the presence at these sites of cell bodies, the activation of which was responsible for the changes observed in the mucosa. That such local stimulation of autonomic elements is possible after traumatic central lesions is demonstrated by the well known frequent instances of hyperthermia following lesions of the hypothalamic region in which the posterior part of the hypothalamus remains intact.

The character of the lesions placed in the present experiments does not allow one to draw conclusions from observations on "acute" preparations in regard to minute localization, i. e., in respect to the specific nuclei. It is to be recalled, however, that the hemorrhagic states occurred spontaneously after complete destruction of the anterior portion of the hypothalamus, whereas craters were never encountered unless part of the anterior part of the hypothalamus was intact. This might

18. Retan, G. M.: J. A. M. A. **105**:1333, 1935.

19. Light, R. U.; Bishop, C. C., and Kendall, L. G.: J. Pharmacol. & Exper. Therap. **45**:227, 1932.

20. Ferguson, J. H., and Smith, E. R. B.: Am. J. Physiol. **109**:34, 1934.

suggest, particularly in the light of Beattie's [21] exacting experiments, that the hemorrhagic states were precipitated by the activation of the sympathetic outflow (posterior portion of the hypothalamus) and the craters by activation of the parasympathetic outflow (anterior portion of the hypothalamus).

The recognition of the relation of gastric functions to body temperature following the elimination of the hypothalamus is significant not only in aiding one to maintain nonheat-regulating preparations to "chronicity" but particularly in demonstrating an actual effect of the deprivation of the hypothalamus on the gastric functions. This alone is sufficient to explain the significance of the known synaptic connections between the hypothalamus and the autonomic outflows. It is to be expected that all the innervations from this region via the autonomic nervous system are intimately related to the mechanism of heat regulation rather than to other primary functions. One must look to "chronic" preparations in which the hypothalamus is destroyed for the ultimate elucidation of hypothalamic function as a whole.

The consideration of the pathologic processes in the gastro-intestinal tract is of interest. That the actual site of the gastric derangement was in the mucosa of the body of the stomach is obvious from the gross and histologic observations. Whether the pathologic changes in the duodenum were due to similar active derangements of the mucosa or were the result of irritation of gastric secretions is a matter of conjecture. In both situations the old question arises as to what part if any the digestive secretions (the formative process or otherwise) and the resistance of the mucosa played, respectively. Analysis of the stomach contents at autopsy for free and combined acid revealed no high values; however, the presence of food in the stomach was infrequent. Of probable importance was the fact that in general no free acid was found in the presence of the hemorrhagic states, whereas free acid usually accompanied the craters.

That both the hemorrhagic areas and the craters were located predominantly on the crests of the gastric folds and that the craters were observed in animals which lived longer after operation than those with hemorrhagic states suggested that the areas of hemorrhage were the precursors of the craters [22] (figs. 5 and 9 and the protocols for dogs 27 and 29). Thus, at first thought it seemed probable that in dog 29 the stimulating effect of the central lesion ceased after the stomach was

21. Beattie, J.; Brow, G. R., and Long, C. N. H.: Proc. Roy. Soc., London, s.B **106**:253, 1930. Beattie, J.: Canad. M. A. J. **26**:278 and 400, 1932.

22. We committed ourselves to this view in the presentation of the earliest observation at the meeting of the American Physiological Society in 1932. Accordingly, this view has been cited subsequently in several instances.

spotted with hemorrhagic areas, at a time sufficiently long before the death of the animal to allow for the clearing of the involved areas by sloughing and digestion. It is certain that the hemorrhagic areas, such as those shown in figure 4, would form transitory craters if normal gastric functions were abruptly or progressively resumed. As our series enlarged, it was noted that hemorrhagic areas and craters were not seen in the same stomach simultaneously and that the hemorrhagic areas did not show evidence of digestion or the craters evidence of surrounding hyperemia or hemorrhage. These last-mentioned observations clearly raised the question of whether the two end-results might not be precipitated by separate and distinct processes.

It should be stressed that no sign of a nonhealing defect was ever encountered that simulated chronic clinical gastric and duodenal ulcers. As the ulcerations of the mouth healed rapidly simultaneously with the central lesion, it would seem that with the clearing of the central lesion one would not expect the mucosal changes that were precipitated spontaneously to become chronic, except possibly in the presence of recurring hemorrhages or tumors. The possibility is not too remote, however, that in certain instances one might be dealing clinically with pathologic changes in the gastro-intestinal tract akin to those induced by heat in nonheat-regulating preparations. In this phenomenon one would have a mechanism by which healing could be continually or periodically delayed as well as new pathologic lesions periodically precipitated after the central injury had healed.

The degeneration of the liver of dog 84 raises the question whether this condition played any part in the production of the duodenal ulcers. It is believed that herein lies the explanation of the increased dextrose tolerance which has been observed after hypothalamic lesions.[23] Hepatic damage is likewise a possible answer to the infrequent hypoglycemic crises. The final answer to these as well as to other questions raised by this preliminary study remains for further carefully designed experiments.

SUMMARY

Spontaneous hemorrhagic states and formation of craters in the digestive tract encountered after intracranial procedures are described. The central mechanism would seem to be the activation of neural elements by one of the following methods:

1. Alteration in the ventricular cerebrospinal fluid by contamination with blood and débris of the lesion.

23. D'Amour, M. C., and Keller, A. D.: Proc. Soc. Exper. Biol. & Med. **30**:1175, 1933.

2. Local traumatic effects of lesions. The certainty of this method is complicated by the fact that the lesions in every instance encroached on the ventricular system.

The question is raised whether the spontaneous hemorrhagic states were the precursors of the spontaneous craters or whether the two were separate and distinct processes.

Marked changes in the gastric mucosa occurring as a result of heating certain nonheat-regulating preparations are also described. This observation is of physiologic significance because it demonstrates an actual effect of the deprivation of the hypothalamus on gastric functions.

PROTECTION BY PERIPHERAL NERVE SECTION OF THE GASTRO-INTESTINAL TRACT FROM ULCERATION FOLLOWING HYPOTHALAMIC LESIONS

WITH PRELIMINARY OBSERVATIONS ON ULCERATION IN THE GASTRO-INTESTINAL TRACT OF THE DOG FOLLOWING VAGOTOMY

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Characteristic spontaneous hemorrhagic states and crater formation following certain intracranial procedures in the dog have been described.[1] This preliminary series of experiments again verified the observation that intracranial procedures can in some instances precipitate acute antemortem pathologic changes in the gastro-intestinal tract, and it furnished my co-workers and me with several indications of the mechanism whereby the gastro-intestinal changes are produced. In addition, this series has given us our own pathologic material to be used as a control, with which we can evaluate results obtained in further experiments designed to answer the question of mechanism. This is essential since, as pointed out in the previous paper, evaluation of the work of one investigator in relation to that of another has proved difficult if not impossible.

In consideration of the mechanism, a question of prominence is whether the pathologic change in the mucosa is precipitated as a result of an actual disorganization of the nerve supply to the digestive tract or whether it is merely the indirect result of more generalized changes. That other changes were wrought was evidenced by the early death of many of the animals, particularly those having extensive hypothalamic lesions. The striking changes in the liver, as seen in dog 84B, are to be recalled in this connection.

If one assumes that the changes were caused by derangement of nerve supply to the gastro-intestinal tract, one wonders about the nature of the alteration. Was it hyperactivation of one of the autonomic outflows, as has been generally believed by previous workers, or might not the two end-results, the hemorrhagic states and the crater formation, be separate processes, one precipitated by the sympathetic inner-

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1. Keller, A. D., this issue, page 127.

vation and the other by the innervation of the vagus, as was suggested by the results of our preliminary study?

In an attempt to answer these questions it was determined to see whether removal of the vagus or the sympathetic nerve supply to the gastro-intestinal tract would prevent the mucosal changes following intracranial procedures. A lesion placed bilaterally at the general level of the optic chiasm was utilized as the central injury, since in the former series such lesions were the most potent in precipitating changes. Accordingly, in one series of animals the vagus nerves were sectioned in the thorax below the heart, previous to or simultaneously with the placing of a chiasmal lesion. In another series the same procedure was carried out except that the abdominal portions of the sympathetic chains were removed instead of sectioning the vagus nerves.

A major complication in the aforementioned planned experiments was the report that ulceration has followed vagotomy as well as sympathectomy. In the light of the well known chaos in the literature in regard to the type and incidence of ulceration following these procedures, it at once became evident that it was essential for us to have controls for our own operative procedures and postoperative regimens. Accordingly, this report consists of a description of lesions observed in the gastro-intestinal tract in a series in which vagotomy and sympathectomy were performed as well as the observations on groups of animals in which chiasmal lesions accompanied the nerve sections.

INVESTIGATION

Vagotomy.—Bilateral vagotomy was performed through a unilateral opening in the dorsal portion of the seventh, eighth or ninth intercostal space. When the diaphragm was retracted downward, excellent visibility of the esophagus was obtained. With slight manipulation of the esophagus both vagus nerves, with their upper and lower branches, were readily identified. In sectioning the nerve trunks a segment of from 1 to 2 cm. was always removed. In addition, the esophagus was cored of all connective tissue, as were the large dorsal blood vessels, in order to ensure complete section of all possible fibers of the vagus nerves.

Our first group consisted of five dogs in which the vagus nerves were cut in the neck, on the right below the exit of the recurrent laryngeal nerve. All the dogs died of consolidation of the lungs—two in forty-eight hours, one in five days, one in thirteen days and the remaining dog in thirty days after operation. The stomachs of the first three dogs were normal, whereas the mucosa of the body of the stomachs of the last two seemed somewhat hyperemic. The first two animals were operated on in November 1932 and the other three in May 1933.

In the second group of three dogs the vagus nerves were cut in the thorax below the heart (in August 1933). Recovery from the operation was uneventful

except for persistent occasional regurgitation of frothy mucus. Regurgitation of food was never observed. The dogs exhibited excellent appetites and showed no evidence of disturbed nutrition. They were all maintained in an outdoor yard. After several weeks dog 110 B lost weight, owing to a severe attack of mange, and the condition became so bad that the experiment was terminated. The stomach was empty and contracted, and the mucosa was of normal appearance. Dog 128 was starved for three weeks in November, and during the period several specimens of the liver were taken for biopsy. After this the dog gained in weight, and at the time of death the animal was in good condition, though it had not regained its prestarvation weight. The dog was found dead in rigor on Dec. 28, 1933. The lungs were normal. The mucosa of the body of the stomach was involved by a considerable amount of connective tissue scarring as well as

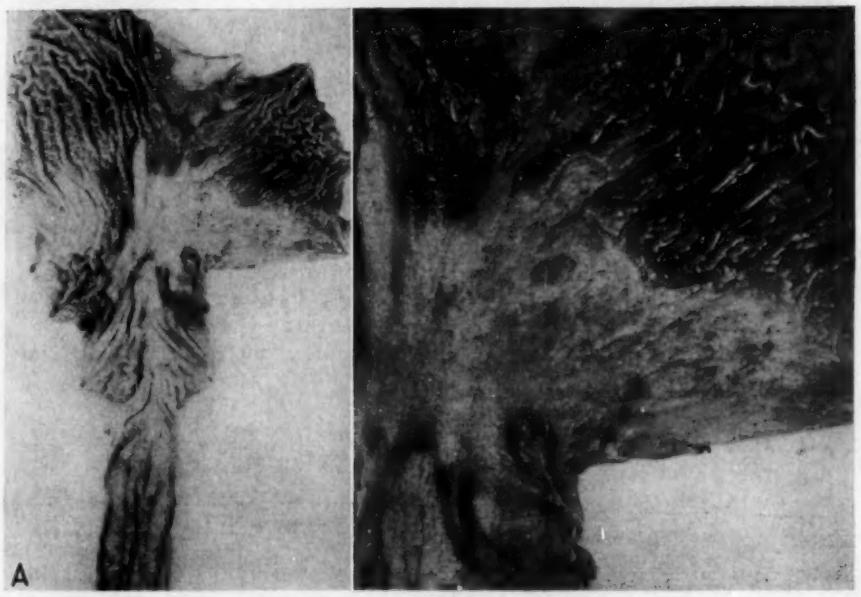

Fig. 1 (dog 128).—*A* is a photograph of the unfixed stomach, showing the huge scarring of the larger portion of the body of the stomach, with well localized acute craters elsewhere, and *B*, a photograph taken with higher magnification of a portion of the stomach shown in *A*, demonstrating the large scar with the well delimited edge of the mucosa.

by acute active localized changes, while some of the mucosa remained in an apparently normal state (figs. 1 and 2). Dog 127 was found dead on Jan. 10, 1933. The thorax was clean, and the lungs were normal. The mucosa of the body of the stomach appeared edematous and red but was unbroken. The pylorus and duodenum were normal.

The next group consisted of six dogs on all of which vagotomy was performed within three days in February 1934. The dogs were placed outdoors in a yard with no special dietary care. They were subjected to external weather conditions except for the protection of an open shed. Three of the dogs died shortly after operation. Dog 228, dying on the fifth day, had normal lungs, but the

mucosa of the body of the stomach showed diffuse slight hemorrhage. The stomach of dog 230, dying on the eleventh day, was not dilated but contained a small amount of leaves and undissolved bone; the mucosa of the body of the stomach and the proximal portion of the pylorus were involved by a characteristic edematous hemorrhagic change, the distal portion of the pylorus and the fundus

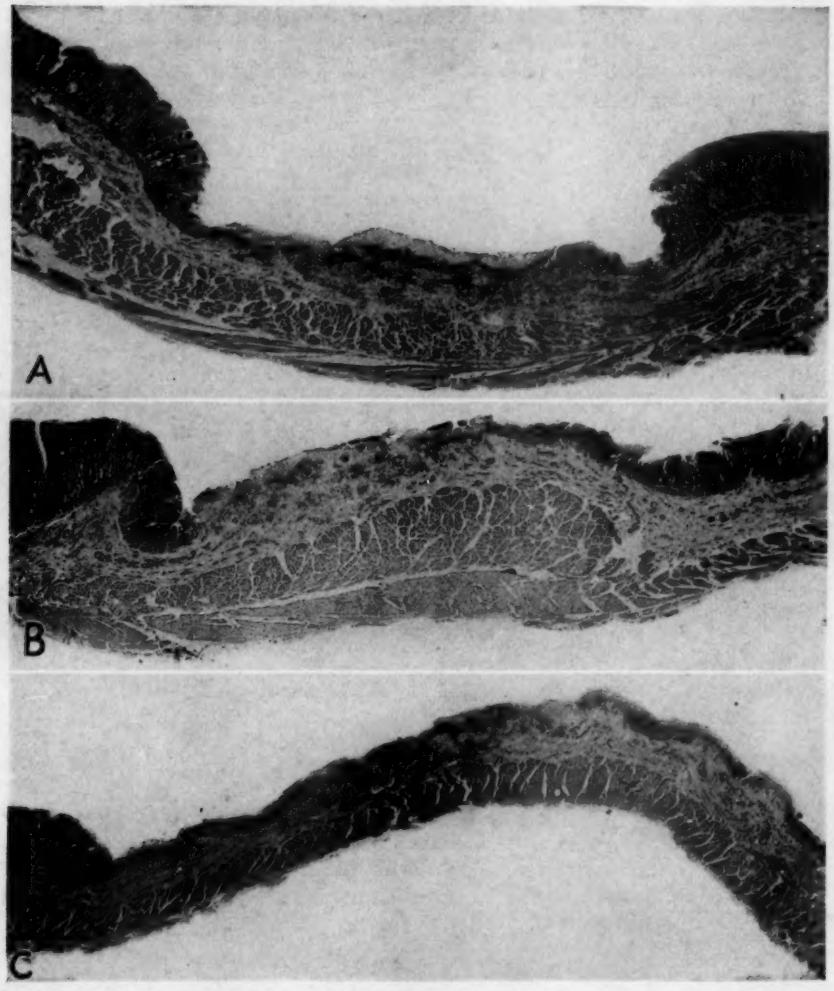

Fig. 2.—Photomicrographs of sections taken from the stomach shown in figure 1. *A* is a section of an acute crater; *B*, a section of a chronic crater, showing even at this magnification the thick-walled blood vessels just below the surface of the scar, and *C*, a section taken through a more extensive area of scarring than that shown in *B*.

being normal (fig. 3 *A*). The lungs of dog 229, dying on the thirteenth day, were consolidated; the stomach contained a small amount of semiliquid food, and the mucosa of the body of the stomach was edematous though not hemorrhagic,

while there was a large shallow erosion in the pylorus. Of the experiments with the remaining three animals, that with dog 225 was terminated on the twenty-fifth day; the dog was in excellent physical condition but since operation had shown a marked appetite and maintained ballooning of the abdomen; the stomach was markedly dilated with food, and in addition to two ulcers induced by the injection of pentobarbital sodium, it presented several small penetrating mucosal craters. Dog 226 died on the thirtieth day; the stomach was contracted and contained no food, and the mucosa was normal. The experiment with dog 227 was terminated on the thirty-second day; the stomach, like that of dog 225, was markedly overfilled with food, straw, hair, etc., but the mucosa was unbroken and normal.

In another group of three dogs, in addition to section of the vagus nerves, the lower part of the thoracic portion of the sympathetic chain was removed bilaterally. The second procedure removed the major splanchnic nerves and

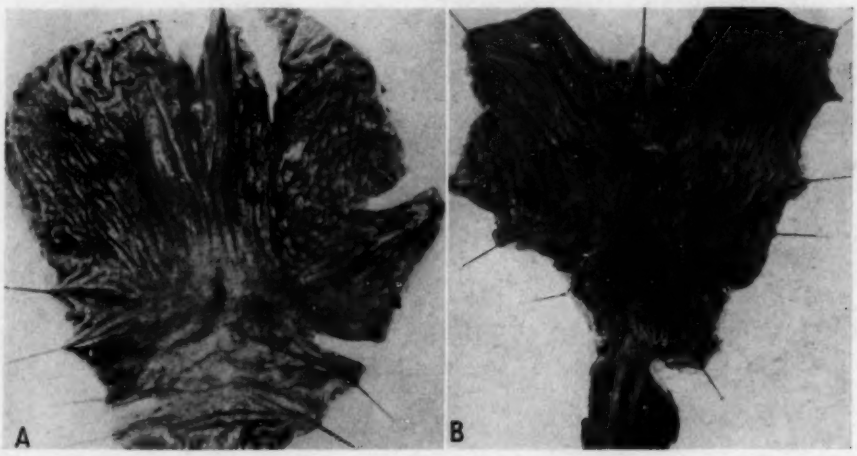

Fig. 3.—*A* is a photograph of the stomach of dog 230 taken after fixation in Klotz' fluid, showing hemorrhagic necrosis of the whole of the body and of the distal portion of the fundus and the proximal part of the pylorus. The unbroken, normal-appearing mucosa of the proximal portion of the fundus and the distal part of the pylorus is evident. The dog died eleven days after bilateral vagotomy. *B* is a photograph of the stomach of dog 223 taken after fixation in Klotz' fluid, showing the marked hemorrhagic involvement of the mucosa of the stomach except that of the extreme distal portion of the pylorus. The dog died eleven days after bilateral vagotomy and bilateral removal of the lower part of the thoracic portion of the sympathetic chain (major splanchnic nerve).

possibly some of the contributory fibers to the minor splanchnic nerves. There are, however, in the dog several large white rami running to the abdominal sympathetic ganglions that are not disturbed by removal of the lower part of the thoracic portion of the chain. Dog 114 B was operated on on July 14, 1933. After operation the animal ate well and maintained an excellent physical condition until just prior to its death, on October 9, from intestinal obstruction caused by lodgment of a corn-cob. The mucosa of the stomach was normal. The remaining two dogs were operated on on Feb. 8, 1934, at the same time as dogs 225, 226,

227, 228, 229 and 230, and were subjected to the same conditions in the yard. Dog 222 after operation maintained excellent physical condition, although ballooning of the abdomen persisted. The experiment was terminated on the thirty-sixth day. The stomach was greatly dilated by food, hair and undissolved bone. The stomach itself showed remarkable hyperplasia, and the mucosa of the body was involved by multiple delimited scarred and acute craters (fig. 4). Dog 223 was found dead on the eleventh day. The stomach was empty, and practically the whole mucosa, including that of the pylorus, was involved by characteristic hemorrhage. The duodenum was hyperemic along the crest of the longitudinal folds (fig. 3 *B*).

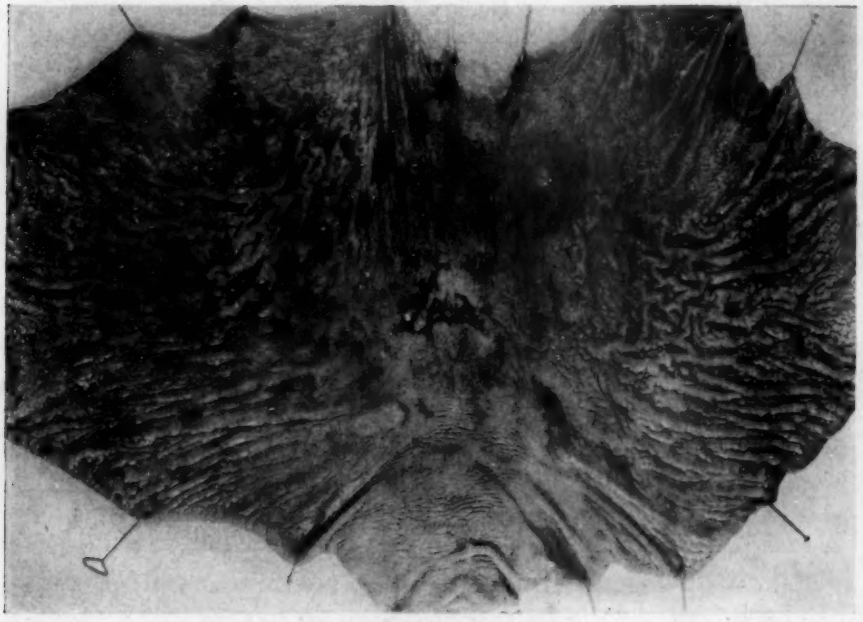

Fig. 4.—Photograph of the stomach of dog 222, showing the enlargement of the whole stomach, several small well delimited scars and sharply demarcated acute craters. The vagus nerves and the lower part of the thoracic portions of the sympathetic chains were removed in this dog.

In another series of experiments performed in collaboration with Dr. G. H. Kistler, vagotomy was performed on twenty-six dogs simultaneously with the injection of pentobarbital sodium into the wall of the stomach through a laparotomy opening. The experiments were designed to determine whether vagotomy delayed the healing of such an artificially induced defect. These experiments were carried out from January to May 1934. Some of the dogs were maintained in cages until the experiments were terminated, from five to ten days after operation, while other animals, because of lack of cage space, were placed outside in the yard. Striking typical acute hemorrhagic changes were precipitated in four of the dogs, whereas early changes were suspected in a few of the others. Of seeming significance is the fact that changes occurred only in dogs which were maintained in the yard and were subjected to extremes of weather.

Summary of Results: A characteristic acute hemorrhagic change in the gastric mucosa (fig. 3) was precipitated in a high percentage of dogs on which vagotomy was performed and which were subjected to yard conditions during the winter months. This change was not precipitated under yard conditions during the summer months or under a cage regimen. In a few instances such acute lesions healed, as evidenced by the extensive scarring in the stomach of dog 128 (figs. 1 and 2) and the well delimited scarring in the stomach of dog 222 (fig. 4). These changes were precipitated when the major splanchnic nerves were removed in addition to vagotomy. The changes were observed in empty contracted as well as in dilated overfilled stomachs, while at the same time empty contracted and dilated overfilled stomachs exhibited no mucosal changes.

The occurrence of persistent regurgitation of frothy mucus but never of food was prominent among the animals of the series and was unassociated with mucosal changes. Overfilling of the stomach occurred in only a relatively few animals in the series, as evidenced by postoperative ballooning of the abdomen and the observation of overfilled stomachs at autopsy. Hypo-acidity was general, as evidenced by greatly delayed dissolving of bone in the lumen of the stomach.

Sympathectomy.—In a series of twenty dogs in which the abdominal portion and the lower part of the thoracic portion of the sympathetic chain were removed bilaterally, there was no evidence of mucosal change at the time the experiments were terminated. The time of termination ranged from twenty-four hours to two weeks after operation. The dogs were not subjected to yard conditions but were maintained under cage regimens. There was no evidence of gastro-intestinal disturbance after operation.

Bilateral Vagotomy Followed by a Chiasmal Lesion.—The aforementioned results of bilateral vagotomy demonstrated that unusual changes did not occur in the dogs which after operation were subjected to ordinary cage regimen. Since the operative procedure of vagotomy does not involve the handling of the gastro-intestinal tract in any way, it was decided to place the chiasmal lesion directly after cutting the vagus nerves, thus limiting the time following the nerve section.

The total number of dogs in this series was twenty-four. Four of the animals died a few hours after operation, before sufficient time had elapsed to determine whether changes would occur. Typical hemorrhagic states were precipitated in nine of the remaining twenty dogs. Gastric or duodenal craters were not encountered in any of the dogs.

The lesions may be listed on the basis of their caudal extent in relation to the chiasm as follows: (1) lesions of the anterior tip of the chiasm, (2) lesions of the midportion of the chiasm and (3) lesions

of the caudal tip of the chiasm. There were six lesions of the anterior tip of the chiasm, six lesions of the midportion of the chiasm and eight lesions of the caudal tip of the chiasm. Hemorrhagic states followed two of the six lesions in the anterior tip of the chiasm, three of the six lesions in the midportion of the chiasm and four of the eight lesions in the caudal tip of the chiasm. Thus, lesions through the caudal half of the chiasm were more effective in causing hemorrhage than those through the anterior part.

Eight of the twenty-four dogs died between twelve and twenty-four hours after operation. In four of these animals bleeding clearly occurred into the lumen of the stomach, while in the remaining four there was no evidence of change. Eight dogs died between twenty-four and thirty-six hours after operation. Five of these animals displayed hemorrhagic states. Four of the remaining dogs died between thirty-six and forty-eight hours after operation, and none showed evidence of gastro-intestinal hemorrhage. Three dogs died during the third day after operation and showed no evidence of gastro-intestinal changes. In dog 430 a bilateral transverse lesion was placed about 2 to 3 mm. anterior to the chiasm. The dog lived until the thirteenth day, when it died as a result of pus in the thorax rather than of the central lesion. The mucosa was normal.

In only four instances in the entire series was there any evidence of blood in the ventricles of the brain. In these cases a small leaf was present in the third ventricle just caudal to the lesion. Three of the four dogs displayed hemorrhagic states.

Seven of the series of twenty dogs exhibited hyperthermia of varying degrees. Bleeding into the lumen of the gastro-intestinal tract occurred in three of these animals, while in the remaining four no gastro-intestinal changes were shown.

In no instance was there gross evidence of involvement of the hypophysis.

The hemorrhagic condition, as evident from gross and histologic examination of the gastro-intestinal tract, was similar to that encountered in our preliminary series. Figure 5 is a photograph of the stomach of dog 262 after fixation in Klotz' fluid. The specimen illustrates mucosal hyperemia with bleeding into the lumen of the stomach, without any histologic evidence of hemorrhage into the mucosa. The hyperemia was sharply limited to the body of the stomach and the duodenum. Figure 6 consists of photomicrographs of sections of the stomach of dog 267. The typical early surface involvement is apparent in *A*, and an area of marked surface hemorrhage in *B*. The different degrees of localized hemorrhage that may occur in the same stomach are evident in these photographs, which readily explain the characteristic variable blotchy gross appearance of the mucosa in such specimens.

Sympathectomy Followed By a Chiasmal Lesion.—In this series the sympathetic chains were removed several days previous to the placing of the chiasmal lesion. At the outset the complete abdominal portion and the caudal part of the thoracic section of the chains were removed. In the later part of the series the thorax was not opened, the abdominal portions of the chains alone being removed, with section of all the splanchnic nerves. The sympathetic chains were removed in their

Fig. 5.—Photograph of the stomach of dog 262 after fixation in Klotz' fluid, showing the more intense hyperemia of the body of the stomach than of the fundus. Free blood was present in the lumen, but the mucosa showed no hemorrhage. Bilateral vagotomy was performed simultaneously with the placing of a chiasmal lesion.

entirety except the cervical sympathetic ganglions in three dogs of the group.

In this series there were thirty-five dogs. Six of the animals did not live sufficiently long to determine whether mucosal changes would have occurred. In fourteen of the remaining twenty-nine dogs, either gastric or duodenal craters were precipitated. Hemorrhagic states were not encountered in any of the group.

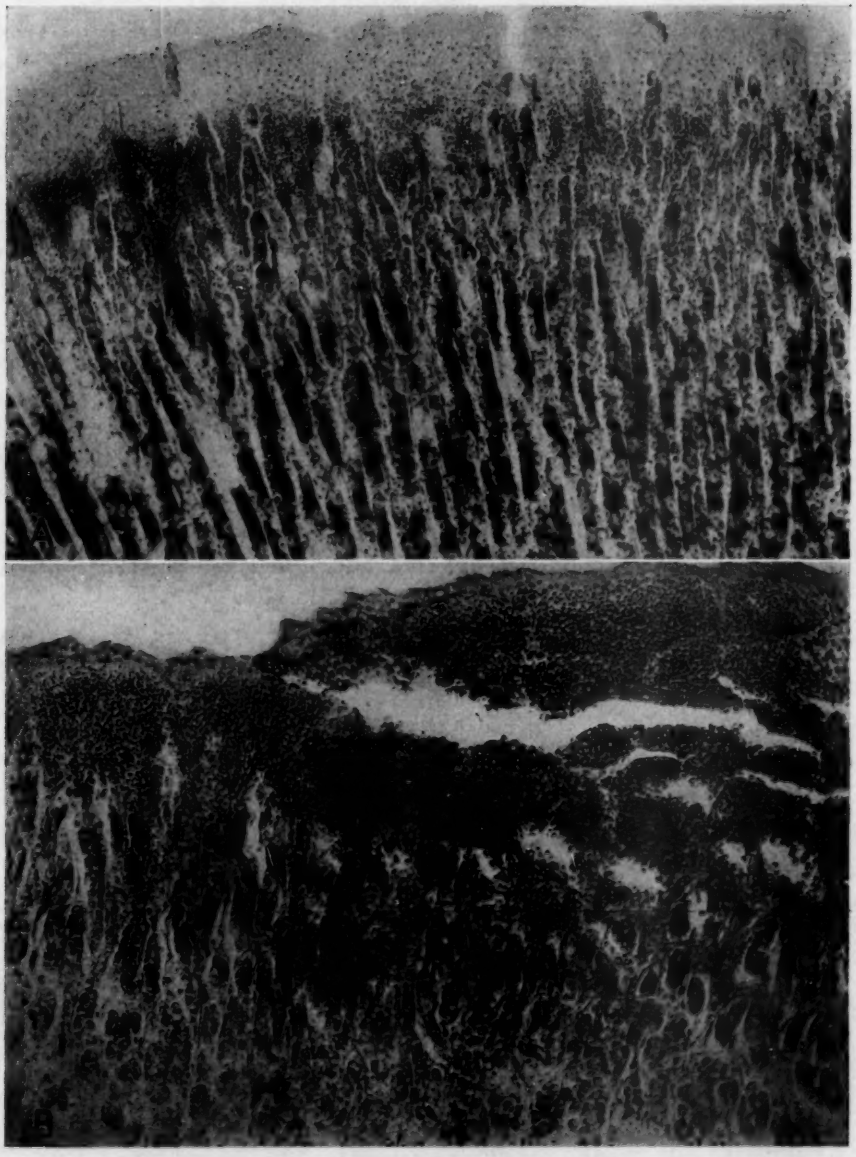

Fig. 6.—Photomicrographs of sections taken from the stomach of dog 267. In this dog bilateral vagotomy was performed simultaneously with placing a chiasmal lesion. *A* shows the surface engorgement of the vessels and the normal gastric cells, and *B*, an area of intense surface hemorrhage.

The central lesions in the dogs with erosions were placed as follows: through the caudal tip of the chiasm in nine dogs, in the midportion of the chiasm in three and in the anterior tip of the chiasm in two. From the results obtained in these animals there is no doubt that the lesions through the caudal level of the chiasm were more potent in precipitating erosions when the abdominal portions of the sympathetic chains were removed. It is to be recalled that in the preliminary series craters occurred only after lesions in the anterior tip of the chiasm. The question arises whether without nerve section these lesions would have precipitated hemorrhagic states.

As already stated, six of the thirty-five dogs died within twenty-four hours of placing the chiasmal lesion. Thirteen died on the second day after operation, seven having mucosal craters. Two of the remaining sixteen dogs died after the ninth day of causes other than the central lesion, while the other fourteen animals died from the third to the seventh day. In seven of these animals craters were present, while in 5 no mucosal changes occurred.

Six of the group of thirty-six dogs exhibited hyperthermia. In four of these animals no mucosal change was shown, while in two craters were exhibited.

Although all the lesions cut across the third ventricle so that the débris of the lesion was accessible to the cerebrospinal fluid, there was free blood in the ventricles in only five of the thirty-five dogs. Gastric craters occurred in only one of these animals, the gastrointestinal mucosa being unbroken in the remaining four.

An amount of gastric contents sufficient for analysis was infrequent as a rule; when free acid was present the value was higher than that for combined acid. In the cases of erosion in which a specimen of contents was obtained, free acid was always present though not in high concentration. For example, analysis of the gastric contents of dog 376 (with a crater of the duodenum) revealed 38 degrees of free acid and 20 degrees of combined acid, or 58 degrees of total acid; of dog 377 (with a gastric crater) 42 degrees of free acid and 15 degrees of combined acid, or 57 degrees of total acid, and of dog 335 (with the mucosa intact) no free acid and 60 degrees of combined acid. It must be stressed, however, that the number of our observations is not sufficiently large to determine whether this pattern is always obtained.

It is noteworthy that accompanying crater formation in the duodenum there were either pyloric craters or well delimited attached blood clots in the pylorus, whereas in only one instance were there craters in the body of the stomach. The photographs of the stomach and duodenum of dogs 308 and 376, respectively (fig. 8), show almost duplicate conditions. The absence of duodenal involvement in the presence of multiple craters of the body of the stomach, as in dog 305,

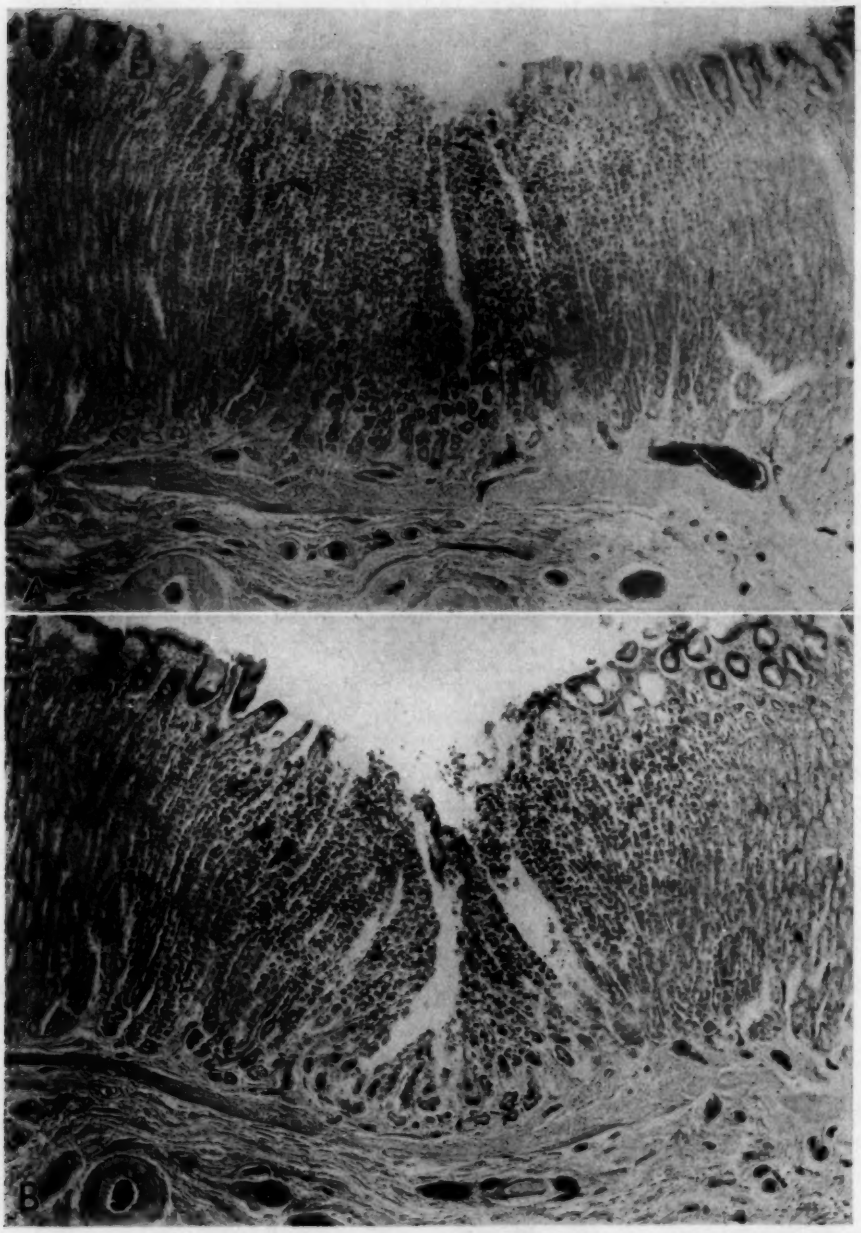

Fig. 7.—Photomicrographs of sections taken through a crater of the stomach of dog 305. The complete sympathetic chains were removed prior to the placing of the chiasmal lesion.

is no less striking. The whitish, wrinkled appearance of the gastric mucosa was constant in all instances, regardless of the location of mucosal defects. The protocols for dogs 305, 308 and 376 are typical.

Dog 305.—The complete left sympathetic chain, except its cervical extension, was removed on June 1, 1934, the right trunk having been removed previously. The chiasmal lesion was placed on June 25, 1934.

Postoperative Observations.—First Day After Operation: The temperature was 34.5 C. (94.1 F.). There was slight shivering. The dog exhibited activity in getting to its feet and walking about the room but showed no excitement.

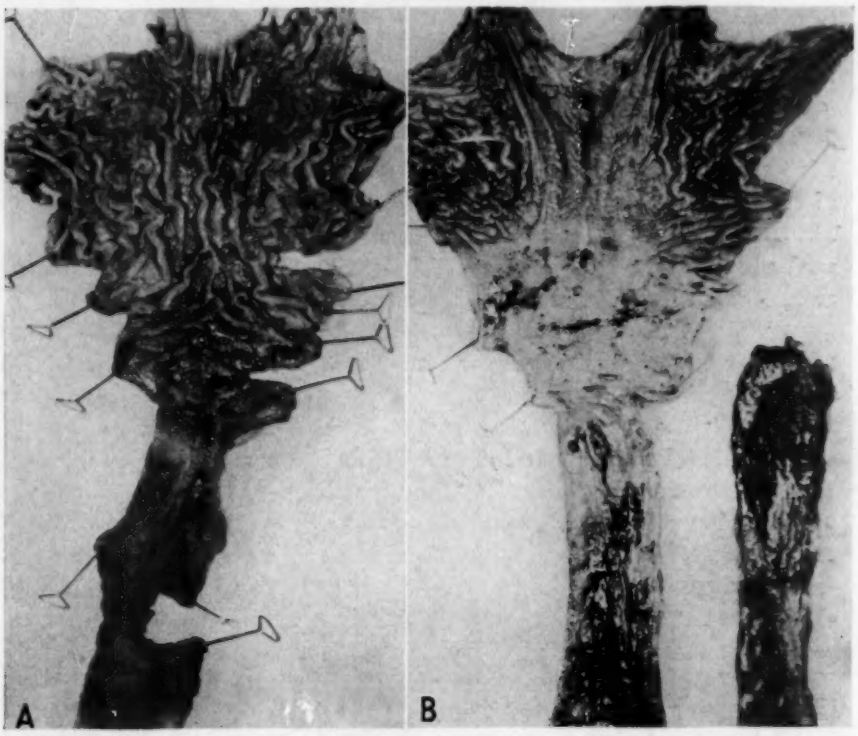

Fig. 8.—Photographs of the unfixed stomach of (*A*) dog 308, showing the whitish appearance of the mucosa of the body of the stomach, the attached blood clots in the pylorus and the crater of the duodenum with neighboring involvement, and (*B*) of dog 376, showing the attached blood clots in the pylorus, unassociated with hyperemia (precursor of pyloric craters), and the duodenal craters.

Second Day: The picture was the same as that on the preceding day. The dog was given milk by stomach tube and did not vomit.

Third Day: The condition was essentially the same as that on the preceding days, except that the animal vomited the milk when fed.

Fourth Day, Morning: The dog vomited the milk when fed.

8 p. m.: The dog was gasping.

Autopsy.—The mucosa of the body of the stomach was involved by multiple small craters (fig. 7). There were none in the pylorus, but one was noted on the duodenal ring. The whole mucosa of the stomach was blanched.

Dog 308.—The abdominal portion and the lower part of the thoracic portion of the sympathetic chain were removed bilaterally on May 3, 1934. A chiasmal lesion was placed on May 10, 1934.

Postoperative Observations.—May 3, 9 p. m.: The temperature was 35 C. (95 F.). No shivering was evident.

First Day After Operation: The temperature was 31.5 C. (88.7 F.). There was no shivering. The dog was not on its feet but kicked periodically.

Second Day, 7 a. m.: The temperature was 28.2 C. (82.8 F.). There was no shivering.

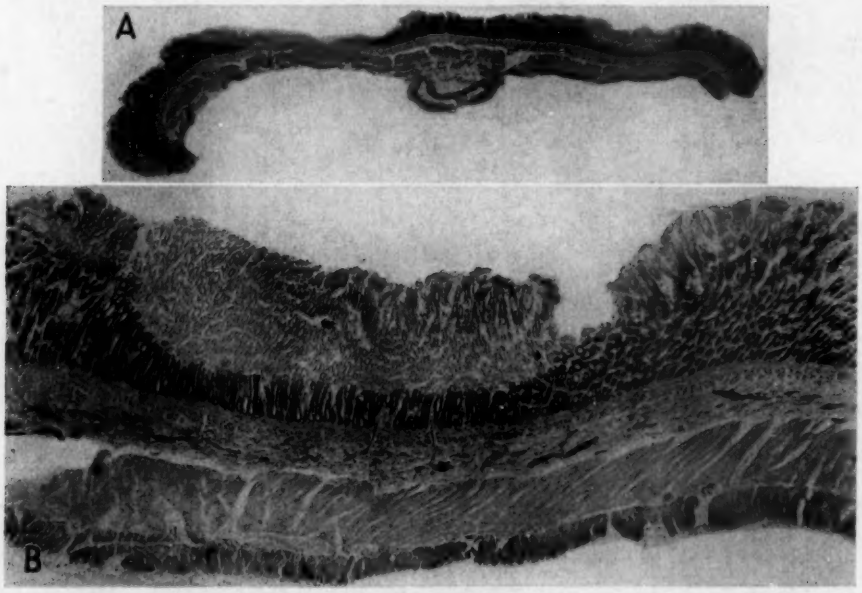

Fig. 9.—Photomicrographs of the duodenal craters in dog 308. *A*, taken under low magnification, shows both craters, and *B*, taken under higher magnification, one crater. The sharp line of demarcation between the vital and the devitalized tissue is evident.

9:15 p. m.: The dog had just died. The lungs were normal. The mucosa of the stomach was characteristically whitish.

Autopsy.—There were no defects in the mucosa, but well delimited blood clots adhered to the mucosa of the pylorus. The proximal portion of the duodenum was involved by two large craters with whitish centers—one round, the other elongated, which looked as though it was made up of two small defects overlapping each other (fig. 8*A*).

Dog 376.—The abdominal portions of the sympathetic chain were removed on June 27, 1934. A chiasmal lesion was placed on June 29.

Postoperative Observations.—June 29, 10 p. m.: The temperature was 38 C. (100.4 F.). The dog was shivering.

First Day After Operation: The temperature was 40 C. (104 F.). The dog was shivering slightly.

Fifth Day, 7 a. m.: The temperature was 34 C. (93.2 F.). There was no shivering. The dog had not been fed since operation.

11 a. m.: The dog had just died.

Autopsy.—The lungs were normal. Analysis of the watery fluid in the stomach revealed 38 degrees of free acid and 20 degrees of combined acid. There was a characteristic whitish appearance of the mucosa of the stomach. There were no breaks in the mucosa of the body but well delimited attached blood clots in the pylorus. The proximal portion of the duodenum was involved by twin craters, one rather round, the other elongated and narrow (fig. 8 *B*).

That the gastric and duodenal craters are identical with those seen in the preliminary series is evidenced by the results of the gross and histologic studies, as shown in the photographs (figs. 7, 8 and 9). The nonhemorrhagic nature of the duodenal defects is particularly well demonstrated by the photomicrograph of a section of the duodenum of dog 308, shown in figure 9.

COMMENT

Vagotomy.—The changes in the gastric mucosa encountered after vagotomy are striking. That the acute process is fundamentally one of hemorrhagic necrosis, which in instances seems to be preceded by edema, is evident in the photographs shown in figure 3. In the event that death does not occur during the first onset of acute changes, punched-out craters form (fig. 2 *A*), which subsequently heal by becoming filled with connective tissue and by the delayed return of normal mucosa (figs. 1 and 2 *B* and *C* and 4). The great range in the size of an area of involvement is well demonstrated in figures 1 and 4. It borders on the miraculous that a dog could live and maintain its weight with a stomach so involved as that of dog 128 (fig. 1).

That changes occurred only in dogs subjected to yard conditions is of physiologic significance in indicating the probability of one's gaining much fruitful information regarding the autonomic nervous control of the involuntary organs by denervation studies on animals subjected to the stress and strain of an unrestricted environment rather than on those living under cage regimen. The results of these studies on the dog warn the clinician, at least in a problematic way, against bilateral vagotomy, unless the patient's environment can be well controlled.

The environmental factor responsible for precipitation of the change would seem to be that of cold weather, though the lack of food intake and overactivation of the sympathetic outflow, such as might result from rage, are probable factors that need careful investigation. Starvation was prominent in the instance of dog 128, whereas no record of food intake was made for the other dogs. That rage was the precipitating factor seems unlikely in that the first three dogs kept in the

yard survived the summer months with no evident disturbance. Likewise, subsequently two dogs taken from the stock pen because of their extreme pugnaciousness were maintained in cages after vagotomy and were markedly enraged by teasing several times daily, for half-hour periods, for weeks, with no effect on the gastro-intestinal tract. That the changes can occur in the absence of the lower part of the thoracic chain (major splanchnic nerves) is evident from observations on dog 222 (fig. 4). This operation, of course, leaves the abdominal portion of the chain intact and, as reported in a previous section, allows the precipitation of the hemorrhagic states following a chiasmal lesion.

One cannot tell at present whether the acute hemorrhagic changes following vagotomy are related to the hemorrhagic states following intracranial procedures, although this possibility arises, as the sympathetic chain is intact in both instances. If the pathologic change is due to the presence of the sympathetic innervation, sympathectomy should prevent such changes. On the other hand, if the pathologic change is precipitated primarily because of the absence of the vagus nerves, sympathectomy should not protect the mucosa from ulceration.

Sympathectomy.—The results for our control group of animals on which sympathectomy was performed need no comment so far as the present experiments are concerned; however, observations on a dog from another series opened the possibility of the precipitation of typical twin duodenal ulcers under conditions of stress following sympathectomy. The abdominal portion and the lower part of the thoracic portion of the sympathetic chains of dog 104 were removed on July 14, 1933. The animal was quartered in the yard with dog 128, and under the same conditions. Dog 104 showed no deviation from the normal. On Jan. 30, 1934, total hypophysectomy was attempted. The dog survived the operation, gained weight and again showed no deviation from the normal. It was found dead on June 1, 1934. Typical acute duodenal ulcers as well as shallow craters in the pylorus were exhibited. It is true that we have encountered such ulcers after hypophysectomy, but, as I shall point out in detail in a subsequent paper, the evidence suggests that the ulcers are precipitated in these instances as a result of opening the third ventricle and not of hypophysectomy. I suspect that in this instance the craters were produced as a result of uninhibited activity of the vagus under a yet unrecognized condition of stress, although the hypophysectomy complicated the picture.

Lesions of the Chiasma.—The results obtained in experiments of this category leave no room for doubt that vagotomy does not protect the gastro-intestinal mucosa from the hemorrhagic states and that sympathectomy does not protect it from crater formation. It would likewise seem that it was not a coincidence that no craters were encoun-

tered in the series of animals subjected to vagotomy and no hemorrhage in the series subjected to sympathectomy and, accordingly, the conclusion that vagotomy protects the mucosa from crater formation and sympathectomy from the hemorrhagic states is probably justifiable.

If one assumes that this conclusion is correct, one can state that the localized hemorrhages are not precursors of the craters and, accordingly, that the two conditions, hemorrhage and craters, are the result of separate and distinct mechanisms. The gross and histologic sections of the gastric and duodenal craters are convincing in this respect, without resorting to nerve sections. That the hemorrhages are precipitated by the activation of a component of the sympathetic outflow and the craters by that of the vagal outflow is strongly suggested by the fact that the section of neither nerve trunk protected the animals from deterioration in the usual postoperative period.

We believe rather strongly that one is dealing in this case with specific activations of the nature of the hyperthermia that occasionally follows a lesion in the hypothalamic region, provided the posterior portion of the hypothalamus remains intact. The reason that one central lesion excites hyperthermia and another, which seems identical, does not has troubled all investigators. The same situation applies in the present instances of precipitation of mucosal changes.

Although it is suspected that the central mechanism for activation of these components is a central local one, one cannot rule out the possibility of stimulation via the cerebrospinal fluid, since all the lesions, with no exceptions, penetrated the third ventricle. It is to be noted, however, that actual bleeding into the ventricle occurred only in a few instances in the complete series and that mucosal changes were present in only a few of these.

A striking difference between the results in this series and those in the preliminary study concerned the location of lesions precipitating erosions. Although lesions through the anterior tip of the chiasm (anterior portion of the hypothalamus) precipitated erosions (in two instances), the majority of the changes and the most striking were produced by lesions cutting through the caudal tip of the chiasm, thus essentially eliminating the anterior part of the hypothalamus. This may indicate that the representations of the sympathetic and the vagus nerves in the hypothalamus are not separated abruptly but are intimately intermingled, with a predominance of the sympathetic elements in the posterior portion of the hypothalamus and a corresponding predominance of the components of the vagus in the anterior portion, as indicated by Beattie's exacting experiments on stimulation. As pointed out in a previous paper, the presence of the chief central heat-regulating mechanism in the hypothalamus readily explains the reason for the presence in this

region of neural elements having synaptic connections with both autonomic outflows. Certainly, the heat-regulating mechanism necessitates synaptic connections with both autonomic outflows.

The results of the few analyses of the gastric contents confirm those for the preliminary series, namely, the absence of high values, the absence of free acid in the presence of the hemorrhagic states and the association of free acid and craters. The relatively low values for combined acid in the presence of the craters may be of significance. It seems noteworthy that the mucosa of the body of the stomach of two dogs killed after repeated doses of pilocarpine displayed fairly marked hyperemia confined to the body with no bleeding, which simulated the early stage of hyperemia of the hemorrhagic states. On the other hand, after administration of repeated doses of histamine to two dogs, the mucosa of the stomach was unusually blanched, and multiple pinpoint hemorrhages in the pylorus were present, thus strikingly simulating in miniature the picture seen in instances of craters.

In the literature on experimental investigations, there is a distinct preference for the theory that hemorrhages are precursors of the craters. Schiff,[2] Ebstein,[3] Burdenko and Mogilnitzki,[4] Cushing [5] and Watts and Fulton [6] were outspoken in favor of this view. Yet it is clear that in nearly every instance craters were encountered in the absence of hemorrhage. One wonders if Brown-Séquard [7] did not suspect that the two processes were distinct. The probability of craters forming without preceding hemorrhage has, of course, long been a prominent theory of ulcer formation, i. e., through spasm of the blood vessels. On the other hand, there is no doubt that the presence of a crater is a stage in the clearing of a hemorrhage.

In considering the relation of injury of the central nervous system to the pathologic changes in the gastro-intestinal tract, Schiff [2] stated: "The connection which exists between these distant lesions has been perfectly grasped in supposing that they are transmitted by the nervous system." It is evident that the possible paths for this transmission from the central nervous system to the gastro-intestinal tract held the interest of all investigators. Schiff's theory of the association of the pathologic change with a component of the sympathetic outflow was at variance

2. Schiff, M.: Leçons sur la physiologie de la digestion, Florence, H. Loescher, 1867.

3. Ebstein, W.: Arch. f. exper. Path. u. Pharmakol. **2**:183, 1874.

4. Burdenko, N., and Mogilnitzki, B.: Ztschr. f. Neurol. u. Psychiat. **103**:42, 1926.

5. Cushing, H.: Surg., Gynec. & Obst. **55**:1, 1932.

6. Watts, J. W., and Fulton, J. F.: Ann. Surg. **101**:363, 1935.

7. Brown-Séquard, C. E.: Progrès méd. **4**:135, 1876.

with previous views, as is evident from the following passage: "The great sympathetic nervous system not having at this time been stripped of its rôle as an independent system, one was forced in good faith to place the path of this curious transmission in the pneumogastric nerves." He expressed the belief that the changes in the gastro-intestinal canal were primarily due to the central paralysis of the vasotonic mechanism. Brown-Séquard [7] agreed with Schiff that the vagus nerves were not the pathway, but he was emphatic in questioning whether a vasomotor disturbance was primarily responsible. It would seem that Burdenko and Mogilnitzki [4] suspected both autonomic outflows, since they spoke of a general disturbance in all of the "chemicophysical" processes; however, they were outspoken in concluding that the hemorrhage which they had observed was due to active vasodilatation produced by the central lesion. They localized the vasodilator mechanism of the cephalic portion of the brain stem in the corpus Luysi. Cushing,[5] though he stated that the outflow responsible still remained to be demonstrated, rather leaned to the theory of the vagal route. Watts and Fulton [6] suspected primary involvement of the vasomotor mechanism via the sympathetic outflow.

The results presented in this paper, as pointed out previously, indicate that both autonomic outflows were concerned in precipitating the changes which we encountered, that is, the hemorrhagic states via the sympathetic nerves and crater formation via the vagus nerves. Although vasomotor disturbances certainly occurred in both instances, namely, engorgement of the vessels with the hemorrhagic states and spasms of the vessels with crater formation, it seems certain that these reactions were secondary to the primary disturbance. That neither the hemorrhagic states nor crater formation was due to generalized vasomotor paralysis is evident from the fact that these changes did not occur after bilateral sympathectomy. Nor were they due to generalized active vasodilatation, since animals in which such a state occurred and persisted for days [8] showed no gastro-intestinal changes. The clear limitation of the hyperemia and bleeding and crest craters to the body of the stomach (area of secretion) suggests that the primary derangement was a disturbance in the secretory process.

It is to be noted that the question raised in the preliminary report as to whether the changes in the liver could have participated in precipitating those in the duodenum is answered in the instance of dog 203, since in this animal typical craters were formed two days after operation. Duodenal ulcers which form in instances of ligation of the bile duct appear only after several days or weeks.

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8. Keller, A. D., and Hare, W. K.: Proc. Soc. Exper. Biol. & Med. **29**:1069, 1932.

SUMMARY

Acute and chronic ulceration in the stomach following vagotomy is described. It is noteworthy that striking changes occurred only in dogs subjected to yard conditions during the winter months.

In a series of dogs in which bilateral vagotomy was performed prior to the placing of a chiasmal lesion, typical hemorrhagic states occurred in the same relations of time and with the same frequency as in our preliminary series. Of apparent significance was the fact that in this group no craters occurred.

In another series the abdominal portions of the sympathetic chains were removed prior to the placing of a chiasmal lesion. In this group typical gastric and duodenal ulcers were formed, whereas no hemorrhagic states were encountered.

ULCERATION IN THE DIGESTIVE TRACT OF THE DOG FOLLOWING HYPOPHYSECTOMY

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AND
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The pathologic changes occurring in the mucosa of the stomach and duodenum after experimental chiasmal lesions were in the preliminary report [1] by one of us tentatively assumed to be mediated through the autonomic innervation of the gastro-intestinal tract. A subsequent investigation [2] designed to determine whether this were true has added strong if not conclusive evidence that such is the case. However, the nearness of the glandular hypophysis to the chiasmal lesions made it necessary to investigate any possible relation of a disturbance in this organ to the gastro-intestinal changes. The approach to the problem has in the main been that of a careful study of the gastro-intestinal tract after total hypophysectomy as well as in a small series in which only a part of the hypophysis was removed.

EXPERIMENTAL INVESTIGATION

Operative Procedure.—The method employed for the exposure of the hypophysis has been the same as that for placing hypothalamic lesions. The temporal pole was raised and retracted with slight tension by the use of a broad and rigid spatula. The broad spatula equalized the pressure over a large area and prevented tearing along its edges. The tension placed the infundibulum under slight traction, thus permitting better visualization of the pia between the hypophysis and the hypothalamus, and at the same time it retracted somewhat the large blood vessels from the field of separation.

The removal of the hypophysis was accomplished by the use of three instruments. In the early part of the series the stalk was grasped between the prongs of an ordinary bent coverglass forceps, and with gentle outward traction the hypophysis was pulled free. Later a pair of blunt ear forceps was used because of the better mechanical advantage in getting at the gland. Finally, in order to avoid leaving loose ends, which the blunt separation allowed, a pair of ear scissors was used, the stalk being cut across at the desired location. Although hemorrhage

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1. Keller, A. D., this issue, page 127.
2. Keller, A. D., this issue, page 165.

was occasionally met by the pulling or cutting of an artery on the unexposed under-side, the gland was usually freed by these methods without eliciting bleeding.

After the separation of the hypophysis from the hypothalamus, care was necessary in the manipulation of removing the gland from the fossa to keep the relation of the two portions intact, as the anterior lobe easily pulled free from the posterior lobe. The gland was removed with the two lobes undisturbed by first freeing the attachment to the artery supplying the posterior lobe before the removal of the gland from the fossa was attempted. On removal of the posterior lobe from the fossa there was usually brisk arterial bleeding of short duration from the artery of the posterior lobe.

Effects of Hypophysectomy on Hypoglycemic Crises.—Normal recovery from the anesthesia with no outward signs of dysfunction after operation and the abrupt onset later of the characteristic symptoms of cachexia hypophyseopriva have been described in detail by earlier workers (Cushing and his associates [3] and Dott [4]). More recently, Houssay and Baisotti [5] have with experimental clarity demonstrated that in the main the symptoms of cachexia hypophyseopriva are due to hypoglycemic shock, as demonstrated by extremely low values for blood sugar as well as by rapid recovery from all symptoms following ingestion of food or administration of dextrose. It is clear from Houssay's work, however, that he recognized that in instances typical symptoms of cachexia hypophyseopriva occurred unaccompanied by low amounts of blood sugar and that administration of dextrose did not always produce recovery.

Of our series of twenty-three dogs in which total hypophysectomy was attempted, six died within forty-eight hours after operation without definite verification of the presence of hypoglycemic shock; fifteen exhibited typical hypoglycemic crises from twenty-four hours to twenty-two days after operation, spontaneously or after a short period of withholding food, and the remaining two dogs were resistant in that crises were not precipitated spontaneously but appeared on starvation—in one dog two and one-half months and in the other eight months after operation. Eight dogs of the series recovered from crises on the administration of dextrose, some as many as three times, but they finally died, failing in each instance to respond to the administration of dextrose. It has been our experience that after one crisis frequent feeding or administration of dextrose was necessary for a period of several days before the dog could again withstand crises under the ordinary regimen of cage feeding.

In three of the dogs in the series pancreatectomy was performed prior to hypophysectomy. This procedure was carried out to make

3. Crowe, S. J.; Cushing, H., and Homans, J.: Bull. Johns Hopkins Hosp. **21**:127, 1910.

4. Dott, N. M.: Quart. J. Exper. Physiol. **13**:241, 1923.

5. Houssay, B. A., and Baisotti, A.: Endocrinology **15**:511, 1931.

certain that hypophysectomy actually prevented the hyperglycemia following pancreatectomy. It has long been recognized that frequently dogs with complete removal of the pancreas recover from hyperglycemia spontaneously a few days after operation. Accordingly, it was ascertained that the hyperglycemia was constant and that it persisted before the removal of the hypophysis. The dogs were maintained after pancreatectomy until hypophysectomy by the administration of insulin. The protocols of the dogs follow:

Dog 175.—The pancreas was removed on Nov. 28, 1933. The blood sugar content was as follows: on December 1, 345 mg.; on December 4, 265 mg., and on December 6, 332 mg., per hundred cubic centimeters. The determination was made forty-eight hours after the administration of insulin.

Hypophysectomy was performed on December 7. The blood sugar content was as follows: on December 8, 82 mg.; on December 9, 118 mg., and on December 11, 75 mg., per hundred cubic centimeters.

The dog showed normal alertness, appetite and muscular activity. The body temperature was normal until December 15, when the animal was found off its feet and in convulsions. The rectal temperature was 32 C. (89.6 F.), and the blood sugar content, 54 mg. Dextrose was given subcutaneously immediately after taking blood at 8:30 a. m. When the dog was examined at 4 p. m., it was up and about normally, with a rectal temperature of 38 C. (100.4 F.).

The dog was found dead on the morning of December 18.

Dog 245.—The pancreas was removed on Feb. 28, 1934. The blood sugar content was as follows: on March 6, 400 mg.; on March 12, 357 mg., and on March 13, before hypophysectomy, 332 mg., per hundred cubic centimeters.

Hypophysectomy was performed in the forenoon of March 13. The blood sugar content was 292 mg. at 9 p. m. On March 14 the dog was normal in every respect, with the blood sugar content 157 mg. On the morning of March 15 the dog was off its feet and had a rectal temperature of 36 C. (96.8 F.). It was not shivering. The blood sugar content was 50 mg. The dog died before dextrose was administered.

Dog 246.—The pancreas was removed on Feb. 28, 1934. The blood sugar content was as follows: on March 6, 490 mg.; on March 12, 452 mg., and before hypophysectomy on March 13, 462 mg., per hundred cubic centimeters.

Hypophysectomy was performed in the forenoon of March 13. At 9 p. m. the blood sugar content was 357. On the morning of March 14 the dog was up and alert, with a normal temperature and a blood sugar content of 200 mg. On March 15 it was off its feet and had a temperature of 35.8 C. (96.4 F.), but was not shivering. The blood sugar content was 40 mg. The dog died before dextrose could be administered.

Hypoglycemia has never occurred in any instance in our series in which the posterior lobe was removed and has occurred only infrequently in dogs with partial hypophysectomy. In two instances in which partial hypophysectomy was performed, hypoglycemia was precipitated after a brief period of withholding food shortly after operation, whereas the dogs became completely resistant to a long period of starvation a few weeks after operation. In one of these dogs the third ventricle was not

opened at operation. We assume that the function of the remaining tissue was temporarily deranged; recovery resulted in the later resistance of the dogs. In one instance the whole of the anterior lobe was successfully removed, leaving the posterior lobe with its normal attachment to the hypothalamus—thus the third ventricle was not opened. A typical crisis was precipitated in this dog three weeks after operation by withholding food for two days.

Hypoglycemic crises occurred regularly and with the same frequency as in the series mentioned in the preceding paragraph in thirteen animals in which the abdominal portion of the sympathetic chain was excised bilaterally prior to hypophysectomy, as well as in thirteen animals in which bilateral vagotomy was performed prior to hypophysectomy.

Ulceration of the Gastro-Intestinal Tract.—In the series of twenty-three dogs already referred to, hemorrhage of the gastro-intestinal tract was encountered in five instances at death, which occurred about twenty-four hours after operation. The hemorrhagic changes were, as judged by antemortem bloody mucoid feces and by the gross and histologic changes, of the same nature as those encountered in our series after chiasmal lesions. The hemorrhagic states in the bowel progressed further in these instances than after chiasmal lesions, as evidenced by actual localized sloughing of the mucosa of the small bowel, illustrated in the photograph of the intestine of dog 166 B (fig. 1 *B*). The protocols for dogs 73 and 166 are typical:

Dog 73.—*Description.*—The dog was a small, white, shaggy female.

Operation.—On March 1, 1933, at 3:45 p. m., the hypophysis was removed with a bent coverslip forceps. There was no hemorrhage, and the usual closure was made.

Postoperative Observations.—March 1, 9 p .m.: The rectal temperature was 35.6 C. (96.1 F.). There was no shivering. The dog raised its head but was still well under the anesthesia.

March 2, 8 a. m.: The rectal temperature was 34 C. (93.2 F.). The dog was off its feet but howled when handled. During the night normal formed feces had been passed, with no mucus or blood.

9 a. m.: The dog passed a considerable quantity of bloody mucus.

11 a. m.: The dog was breathing deeply and when picked up began to gasp.

Autopsy.—The thorax was normal except that one lobe of the left lung was consolidated.

The stomach contained watery bloody fluid with small blood clots in suspension.

The mucosa of the body of the stomach exhibited blotchy hyperemia. The whole of the small bowel except the distal tip of the ileum was involved by irregular patches of mucosal hemorrhage.

The pituitary fossa was clean except for a small blood clot. Histologic sections showed that the hypothalamus was intact but that a small bit of the pars tuberalis remained. There was no blood in the third ventricle.

Dog 166 B.—*Description.*—The dog was a large black and white female.

Operation.—On Nov. 22, 1933, complete removal of the hypophysis was attempted. There were excellent visibility and no bleeding. The usual closure was made.

Postoperative Observations.—November 23, 8 a. m.: The rectal temperature was 36 C. (96.8 F.). The dog was shivering and had passed a small amount of feces tinted with fresh blood.

2 p. m.: Milk was given by stomach tube.

5 p. m.: The dog vomited curdled milk and passed feces diffusely filled with fresh blood.

7:30 p. m.: The dog was found dead.

Autopsy.—The thoracic and abdominal cavities were clean. The mucosa of the body of the stomach was spotted with areas of hyperemia and hemorrhage, while the fundus and pylorus were uninvolved. The duodenum and small bowel were markedly hemorrhagic, as shown in the photograph (fig. 1 *B*). The lumen of the small bowel was filled with blood.

The surface of the brain was clean. The pituitary fossa was clear except for a small blood clot. A small clot remained attached to the base of the hypothalamus on removal of the brain. Histologic sections showed that the hypothalamus was intact with no blood in the third ventricle. A bit of the pars tuberalis remained (fig. 1 *A*).

Typical twin duodenal ulcers were observed in four of the twenty-three dogs. In one animal (dog 103) typical craters were present in the body of the stomach (fig. 2). In at least one dog and possibly in two others, early crest craters were present without any definite duodenal change from twenty-four to forty-eight hours after operation. In the four dogs mentioned the duodenal ulcers were present at death or at the termination of the experiment, on the fourth, ninth, fifteenth and sixteenth days after operation. The protocols for dogs 75 and 103 are typical.

Dog 75 B.—*Description.*—The dog was a white and brown spotted female, weighing 6.6 Kg.

Operation.—On March 6, 1933, at 3:30 p. m., the anterior lobe of the hypophysis was removed, the posterior lobe remaining in the pituitary fossa (separated from the stalk but not from the artery of the posterior lobe). Good exposure with the usual closure was made.

Postoperative Observations.—March 6, 9:45 p. m.: The temperature was 36 C. (96.8 F.). The dog was shivering.

March 7, 8:15 a. m.: The temperature was 40 C. (104 F.). The blood sugar content was 125 mg. per hundred cubic centimeters.

March 8, 8 a. m.: The temperature was 38.5 C. (101.3 F.). The blood sugar content was 120 mg. The dog drank 200 cc. of milk, leaving some in the dish.

March 9, 8 a. m.: The temperature was 39 C. (102.2 F.). The blood sugar content was 145 mg. The dog ate a small amount of stock food.

March 10, 8 a. m.: The temperature was 39 C. (102.2 F.). The dog drank 150 cc. of milk, leaving some in the dish.

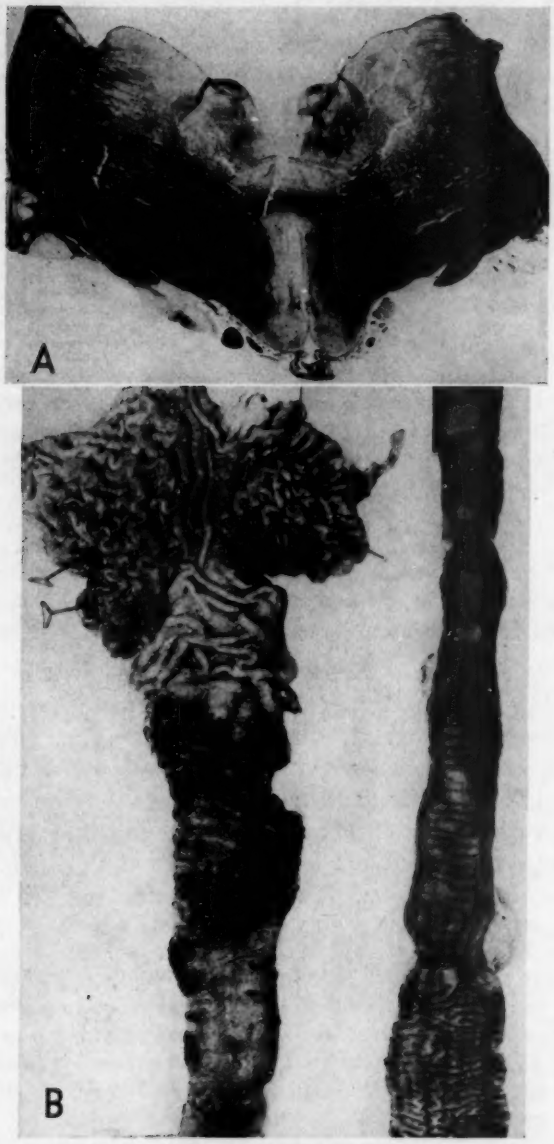

Fig. 1 (dog 166).—*A* is a photomicrograph of a section through the level of the infundibulum, showing (1) the intact hypothalamus, (2) the third ventricle free from blood, (3) the third ventricle opened ventrally and (4) a small bit of the tissue of the pars tuberalis and a blood clot located at the opening of the third ventricle. The blood appears black, whereas the tissue of the pars tuberalis is the lighter material bordering the clot. *B* is the photograph of the gastrointestinal tract taken after fixation in Klotz' fluid, showing (1) the blotchy hyperemia of the body of the stomach without involvement of the fundus and pylorus, (2) the hemorrhagic duodenum and (3) the hemorrhagic ileum with the mucosa adjacent to the sphincter intact.

March 11, 8 a. m.: The temperature was 40 C. (104 F.). The blood sugar content was 87 mg. The dog refused stock food.

March 12, 8 a. m.: The temperature was 39 C. (102.2 F.). The blood sugar content was 100 mg. The dog refused milk.

March 13, 8 a. m.: The temperature was 39 C. (102.2 F.). The blood sugar content was 77 mg. The dog had cleaned up the milk left in the cage.

March 15, 1 p. m.: The temperature was 31 C. (87.8 F.). The blood sugar content was 40 mg.

2:15 p. m.: The dog was gasping.

Autopsy.—The thorax was normal. The abdominal cavity was normal except that the liver was whitish yellow. The stomach was empty. The mucosa was blanched, and there were several delimited whitish areas in the mucosa of the body, with one definite erosion.

The proximal portion of the duodenum was involved by sharply delimited penetrating twin duodenal ulcers (fig. 2*A*). Elsewhere, there was definitely early localized change on the surface of the mucosa, as is readily evident in the photograph. The rest of the bowel was essentially normal.

The surface of the right hemisphere was covered by a sheet of subdural clot, which extended over the temporal pole but did not reach the base. The base of the brain was clean. There was a bit of whitish tissue devoid of form in the pituitary fossa, which was probably the remains of the posterior lobe. Histologic sections demonstrated that the hypothalamus was intact, with a bit of the pars tuberalis left attached.

The histologic description of the liver (Dr. G. H. Kistler) follows:

In the histologic preparations of liver stained with hematoxylin and eosin the tissues were practically entirely replaced with large fat vacuoles—the so-called "signet-ring" cells. These clear spaces were compact so that only thin fibrillar walls separated them, and among them were only a few nuclei, some of which were outside the vacuoles. The central veins of the lobules and the lobular markings were indistinct. Hepatic triads in the sections examined had small blood vessels and the usual bile canaliculi, and about the triads were a few small round cells and larger pale blue cells resembling compressed and atrophic remnants of liver cells. There were no collections of round cells sufficiently great to indicate chronic inflammation. The vessels of the hepatic triads contained a few erythrocytes, but elsewhere there was no blood in the tissues.

Dog 103.—*Description.*—The dog was a brown shaggy female, weighing 4.9 Kg.

Operation.—On June 16, 1933, in the forenoon, the hypophysis was removed, eliciting an arterial hemorrhage, which was soon controlled; however, on closure blood was left at the base of the brain.

Postoperative Observations.—June 16, 3:30 p. m.: The temperature was 36 C. (96.8 F.). The dog was under light anesthesia but was quiet.

9:30 p. m.: The temperature was 36.3 C. (97.3 F.). The dog had righted itself and was quiet.

June 18: The temperature was 37.5 C. (96.5 F.). The dog was up and about but was sluggish and refused food. It was given 200 cc. of milk by stomach tube.

June 19, 7 a. m.: The temperature was 38.5 C. (101.3 F.).

June 20, 9 a. m.: The dog was found dead.

Autopsy.—There was dark blood in the lumen of the stomach and the small bowel. The mucosa of the body of the stomach was involved by multiple

erosions of two types: rather deep craters situated partly in the furrows between the mucosal folds and craters on the crests of the folds, like those observed in dogs 29 and 33 B (described in a previous paper).

In the proximal portion of the duodenum there were large, sharply delimited, penetrating twin ulcers, like those observed in dogs already examined (fig. 2*B*).

The brain was covered with blood on the dorsal surface as well as at the base. Histologic sections showed that the hypothalamus was intact and the hypophysis completely removed.

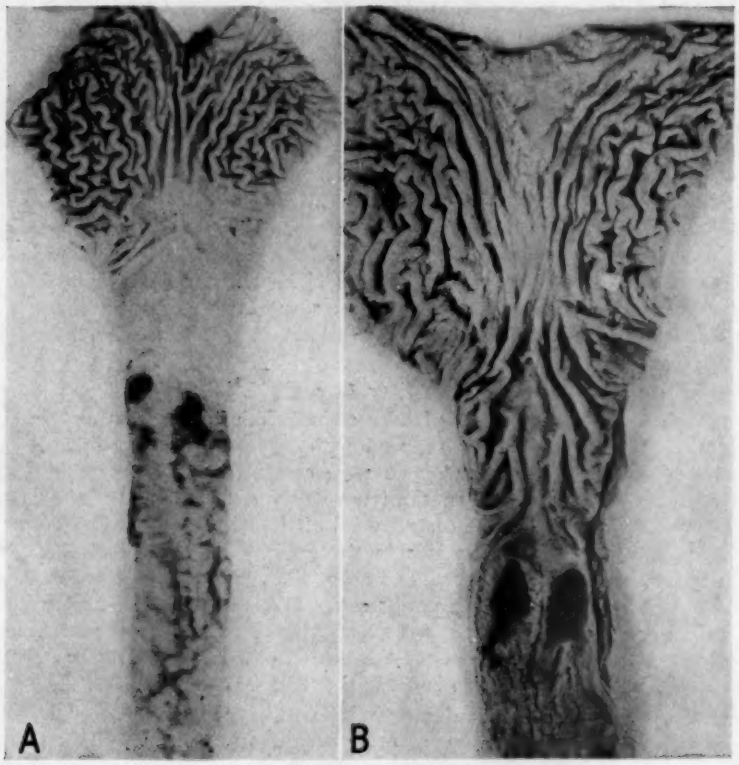

Fig. 2.—Photographs of the stomach and duodenum (*A*) of dog 75 B after fixation in Klotz' fluid, showing (1) the normal condition of the gastric mucosa except for one small crater on a mucosal crest of the body just adjacent to the pylorus and (2) the twin penetrating duodenal ulcers, the one round and the other irregular, with the neighboring necrotic involvement, and (*B*) of dog 103 B after fixation in Maximow's fluid, showing (1) the numerous defects in the mucosa of the body of the stomach, mainly in the region adjacent to the pylorus, and (2) the twin penetrating duodenal ulcers.

Ulceration Following Nerve Section.—In the thirteen dogs in which the vagus nerves were sectioned prior to hypophysectomy, no craters

were encountered. In one instance (dog 203) the mucosa of the body of the stomach was markedly hemorrhagic, as evident in the gross photograph shown in figure 3 and the photomicrograph in figure 4. In this dog complete removal of the hypophysis with no hypothalamic

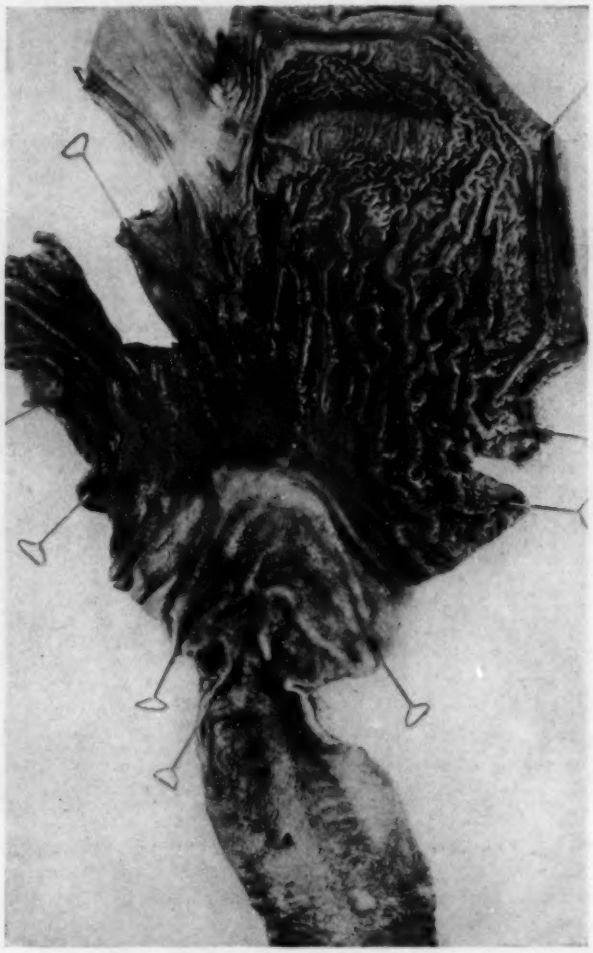

Fig. 3.—Photograph of the stomach of dog 203 B after fixation in Klotz' fluid, showing the marked hemorrhagic nature of the mucosa of the body of the stomach while the fundus, the pylorus and the duodenum are not involved.

involvement is evident in the photographs shown in figures 5, 6 and 7. The protocol for the dog follows:

Dog 203.—*Description.*—The dog was a white shaggy male, weighing 8.5 Kg.

Operation.—The vagus nerves were cut in the thorax below the heart on Jan. 10, 1934. On Jan. 16, 1934, the hypophysis was successfully removed in one piece

and placed in Maximow's fluid.[6] The gland was separated from the brain with one snip of the scissors. Visibility was excellent. Blood from the artery of the posterior lobe oozed on closure.

Postoperative Observations.—January 16, 9:30 p. m.: The temperature was 40.5 C. (104.9 F.). The dog was on its feet though still shaky. It was quiet.

January 17, 7 a. m.: The temperature was 39.5 C. (103.1 F.). There was no shivering. The dog was alert and friendly but refused milk.

January 18, 4:30 p. m.: The dog seemed sleepy. It drank 150 cc. of milk ravenously.

9 p. m.: The temperature was 39.8 C. (103.6 F.).

January 19, 7 a. m.: The temperature was 40 C. (104 F.).

11 a. m.: The dog refused to eat and was given 150 cc. of milk by stomach tube.

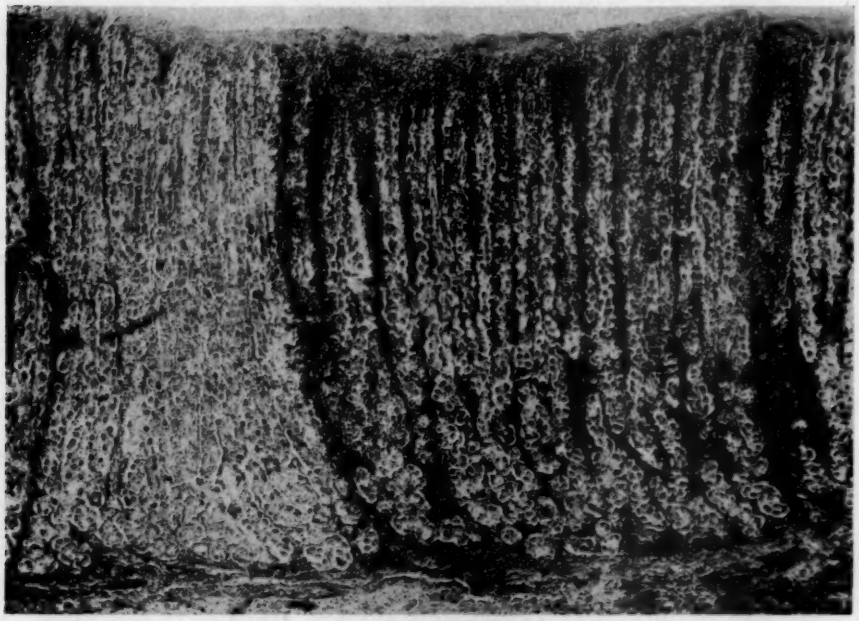

Fig. 4.—Photomicrograph of a section of the mucosa of the stomach of dog 203, showing the area of pronounced hemorrhage extending to the muscularis, with the small isolated uninvolved area. The reason for the sharp separation of the areas is, of course, not known, but it readily explains the blotchy hyperemia and hemorrhagic mucosa observed in the entire series.

4:30 p. m.: The dog refused solid food. It appeared normal except that it was apparently sleepy.

5 a. m.: The dog was found on the floor of the cage in extensor rigidity. It seemed to be conscious but made no attempt to right itself. The temperature was 40.5 C. (104.9 F). Peritonitis was suspected. Blood was taken (the blood sugar content was 59 mg. per hundred cubic centimeters), and dextrose was given

6. Maximow's fluid is a modification of Zenker's solution, with the addition before using of 10 cc. of a 10 per cent solution of formaldehyde per hundred cubic centimeters of fluid instead of 5 cc. of acetic acid.

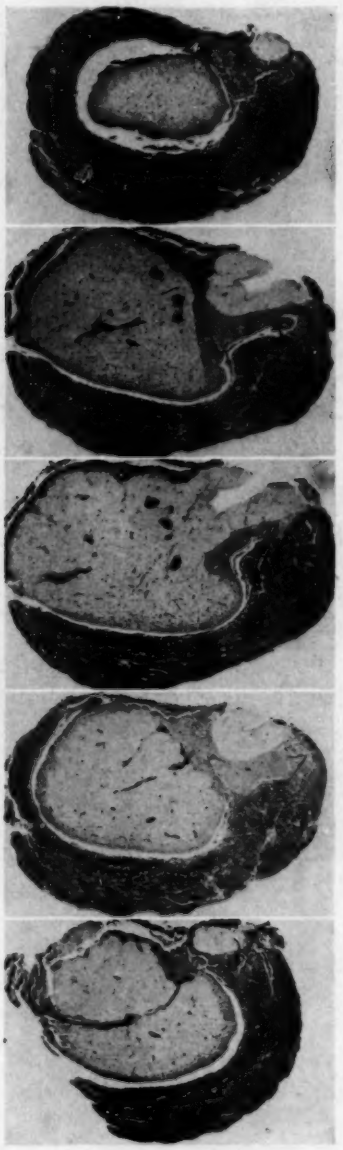

Fig. 5.—Photomicrographs of serial sections of the hypophysis of dog 203, showing the intactness of the whole gland as well as the distal tip of the third ventricle.

subcutaneously. The abdominal muscles were rigid when first examined, but they relaxed completely with slight massage. There was no evidence of pain during examination.

9 p. m.: The dog was found dead.

Autopsy.—The thorax and lungs were clean and normal. The abdominal cavity was normal except that the omentum and pancreas were hyperemic. There was clearly no peritonitis.

As the stomach was opened red fluid escaped. The mucosa of the body was markedly hemorrhagic. The mucosa of the fundus and pylorus was not involved (fig. 3). The duodenum was hyperemic some distance below the sphincter. The lumen of the small bowel was fully of pasty material well mixed with fresh clotted blood.

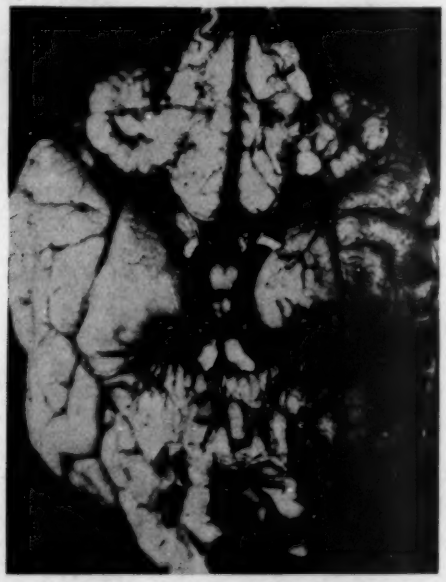

Fig. 6.—Photograph of the base of the brain of dog 203 after hardening in formaldehyde and before removal of the pia and surface vessels, showing the entire freedom from blood except subpial staining about the cephalic part of the ventral aspect of the right hemisphere and the opened third ventricle, which is readily seen even under this magnification.

The brain was clean except for a slight subpial hemorrhage over the anterior extent of the right temporal pole. The base of the brain and the pituitary fossa were clean. The temporal poles were intact, and the third ventricle was open ventrally, as evident in the photograph shown in figure 6, which was taken after the brain had been hardened in formaldehyde and before the surface blood vessels and the pia were removed. Serial sections through the hypothalamus further demonstrated complete removal of the hypophysis as well as the intactness of the hypothalamus except for a small infarct, shown in the photograph (fig. 7 *B*), just medial to the fornix on the right side. The patent third ventricle and the absence of blood in the ventricle are shown in figure 7 *A*.

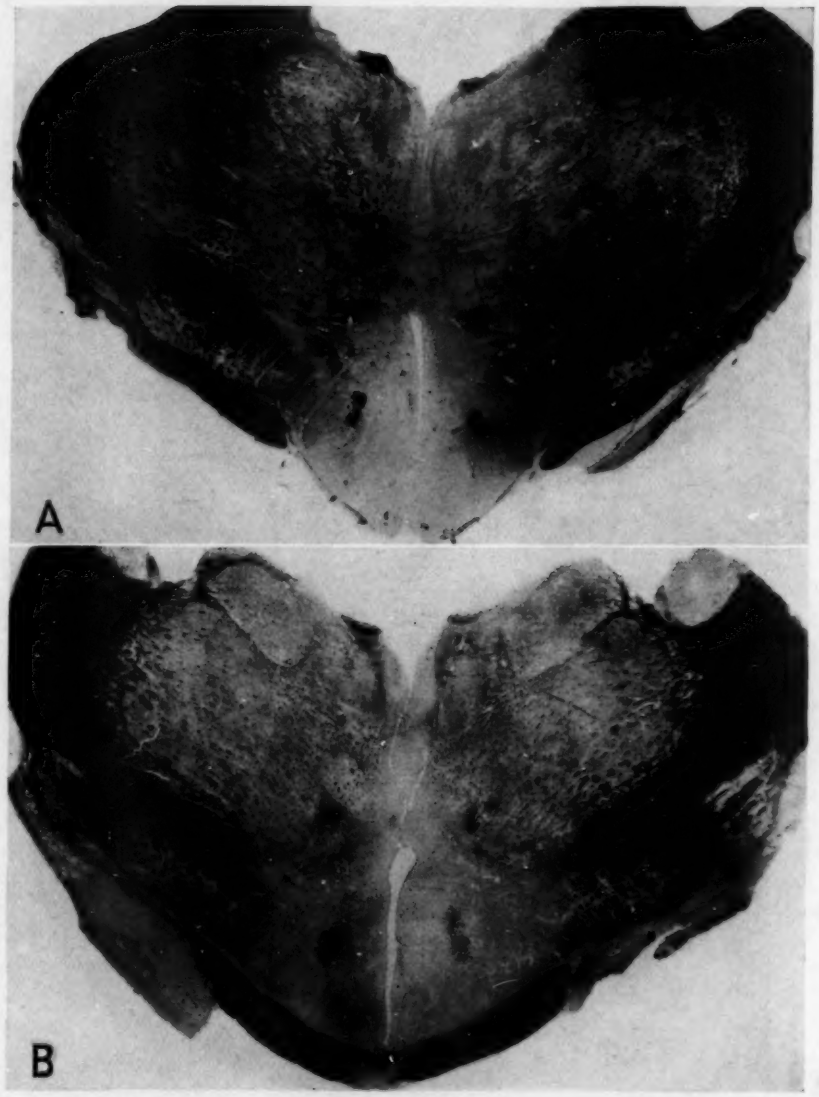

Figure 7.—Photomicrographs of transverse sections through the hypothalamus of dog 203, showing the hypothalamus intact except for a small anemic infarct just medial to the fornix on the right in *B* and the absence of any attached hypophyseal tissue and of blood in the third ventricle.

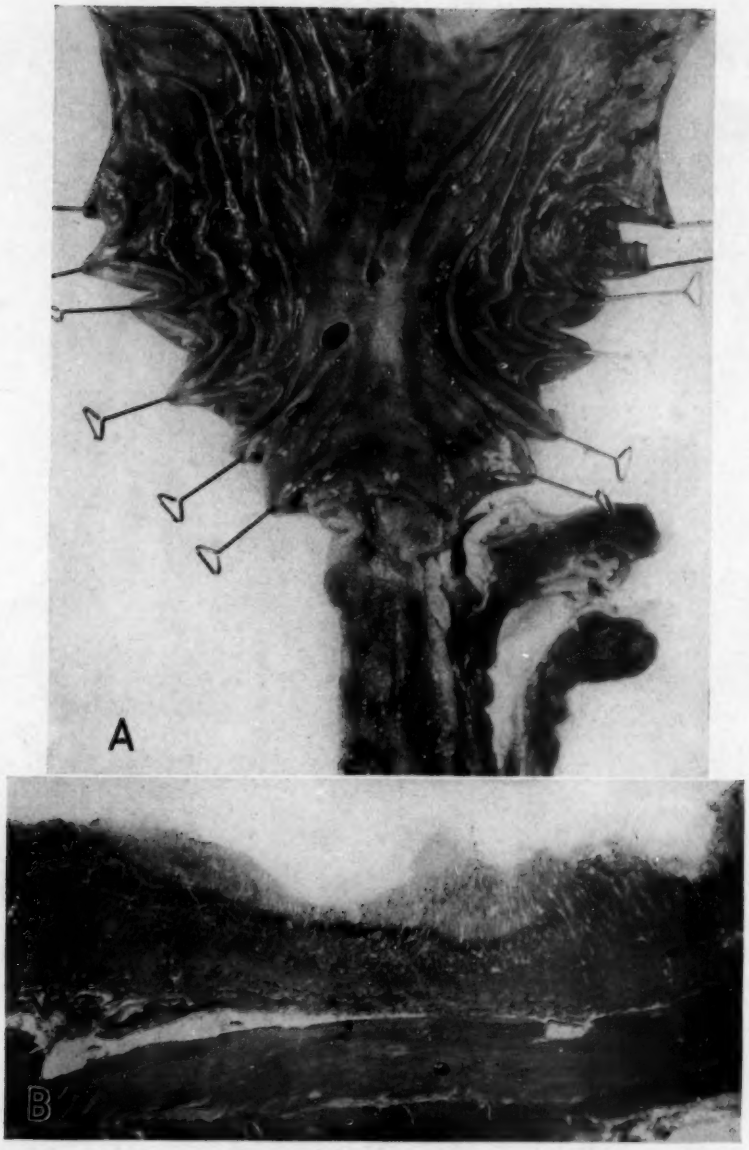

Fig. 8.—*A* is a photograph of the stomach and proximal portion of the duodenum of dog 213, showing the shallow crater in the pylorus and the intense hyperemia of the pancreas, and *B*, a photomicrograph of a section of the proximal portion of the duodenum, showing early crater formation, which does not appear in the photograph of the gross specimen shown in *A*.

In the thirteen dogs in which the abdominal portions of the chains were removed before hypophysectomy, no hemorrhagic states were encountered. Multiple gastric craters, occurring predominantly in the pylorus, were encountered in five of the dogs, with definite duodenal involvement in two instances and suspected early duodenal involvement in the other three (fig. 8). In the majority of this series the hypophysis was removed with bent tissue forceps.

COMMENT

There is no doubt, as is readily appreciated from a comparison of the gross and the histologic tissue (as shown in all the figures in the three papers), that the hemorrhagic states and gastric and duodenal craters encountered after hypophysectomy were identical with those which occurred after chiasmal lesions. Accordingly, it would seem logical to look for the same precipitating cause in both situations.

That the hypoglycemic crises were the result of deprivation of the anterior lobe is evidenced by: (1) the high and regular incidence of verified crises in the entire series of forty-nine animals, (2) the precipitation of crises by withholding food in animals which survived sufficiently long after operation for permanent closure of the third ventricle and (3) the occurrence of crises in two instances in which the anterior lobe was successfully removed without opening the third ventricle.

In contrast to the constant picture of hypoglycemic crises following hypophysectomy, the incidence of mucosal changes in the same series was low and irregular, which would seem to indicate that these effects were caused by other factors than hypophyseal deprivation. We looked to the neighboring brain stem for the explanation of the gastro-intestinal ulceration and suspected accompanying hypothalamic injury even prior to the experiments on nerve sections; however, the absence of such injury has forced us to adopt the only remaining explanation that we can see thus far, namely, the possibility of intraventricular stimulation via the artificial opening into the third ventricle, which occurs as a result of separating the hypophysis from the hypothalamus. It is readily appreciated from a study of the sections shown in figures 5 and 7 that complete removal of the hypophysis is impossible in the dog without encroaching on the ventral wall of the third ventricle.

If one assumes that intraventricular stimulation is the cause, the low and irregular incidence of gastro-intestinal ulceration is readily explainable on the basis of only an occasional optimum patency or, possibly more exactly, of the optimum movement of fluid from the subarachnoid space into the ventricular system, or vice versa. It is, of course, possible that even with a patent opening there might be little or no interchange of fluid between the two systems. Another possibility is filling of the

ventricular system with fluid from the subarachnoid spaces, with subsequent stagnation. There is likewise little doubt that in most instances the opening of the ventral portion of the third ventricle is soon closed by débris and actual clotting of the admixture of blood and cerebrospinal fluid.

In considering more specifically the mechanism of a possible central stimulation, one thinks of (1) a chemical factor, such as (*a*) a specific ionic effect produced by increased concentration of a constituent or constituents normally present or by the presence of foreign constituents or (*b*) a general osmotic effect due to a general change in osmotic concentration, or (2) a possible, but less probable, mechanical factor, such as an abnormal direction or rate of flow.

Two possible sources of contamination of the subarachnoid cerebrospinal fluid at once presented themselves: (1) products liberated directly from the hypophyseal tissue during the process of removal, as well as subsequent deterioration of the remaining tissue of the pars tuberalis (fig. 1 *A*), and (2) the blood and products of blood clotting, which of necessity remained in varying amounts in the operative field. The possibility of the gastro-intestinal ulceration being dependent on central stimulation by hypophyseal products was, however, completely ruled out in the instance of dog 203, in which the gland was completely removed without maceration of any part, as is evident in the photographs shown in figures 5 and 7. On the other hand, the cleanness of the operation in this instance (dog 203) and in others as well as that of the brain and base (fossa) at autopsy has caused us to raise the question, in a speculative way, of the possible effects of the mere shunting of uncontaminated subarachnoid fluid into the ventricular system. In other words, is it possible that the composition of the subarachnoid fluid is sufficiently different from that of the ventricular fluid that the continued presence of the former fluid in the ventricles might excite central elements to abnormal activity?

Other reactions encountered that would seem also to be identified with intraventricular stimulation were slight hyperthermia and mild hyperglycemia; both usually appeared directly after hypophysectomy and sometimes continued for several days. The protocols for dog 75 and 203 are typical. The incidence of these responses was, as would be expected, greater than that for gastro-intestinal ulceration, since it was possible to detect and follow the degree and duration of the effect during the postoperative course. One is also likely to interpret the deaths which rapidly followed the operation with no accompanying hypoglycemia as due to rapid and severe derangement which might result, for instance, from a more active communication between the two systems.

The results of experiments on nerve section clearly demonstrate that vagotomy does not protect the gastro-intestinal tract from hemorrhagic

states and sympathectomy does not protect it from crater formation following hypophysectomy. The series were too small, because of the irregularity in the occurrence of ulceration, to permit any conclusions to be drawn regarding a reversed protection.

SUMMARY

Characteristic hemorrhagic states as well as crater formation were encountered with low and irregular incidence after attempted total hypophysectomy in the dog.

Vagotomy did not protect the gastro-intestinal tract from the hemorrhagic states, or sympathectomy from crater formation.

Evidence is presented which indicates that the ulceration was precipitated not because of the lack of the hypophyseal secretions but because of a neighboring neural derangement, possibly intraventricular stimulation, as a result of opening the third ventricle during the operative procedure.

The possible mechanism of intraventricular stimulation is briefly discussed in a problematic way.

The data obtained on changes following hypophysectomy support the conclusion of previous workers that the hypoglycemic crises are due to deprivation of the anterior lobe of the hypophysis.

ALVEOLAR PORES AND THEIR SIGNIFICANCE IN THE HUMAN LUNG

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In the survey on which the following summary is based fifteen human lungs from persons of both sexes were studied. Thirteen of the lungs were examined microscopically, three hundred sections being cut in different thicknesses (for the most part from 25 to 50 microns or more) and variously stained. The range of ages of the patients was from 2 years and 5 months to 82 years, the specific ages being as follows: 2 years and 5 months and 7, 13, 13, 23, 27, 30, 36, 40, 49, 74, 80 and 82 years. The causes of death were nonpulmonic. In two cases sudden death had resulted from an automobile accident.

The lungs were obtained soon after death and fixed immediately, some in the condition of collapse and others in that of inflation. The collapsed organs were prepared either by cutting out pieces and immersing them in a fixative or by submerging the entire lung in a preservative. Those fixed in the condition of inflation were prepared mainly by the introduction of fixing fluid into the bronchial tree at a moderate pressure, which at first was usually from 4 to 6 inches (10 to 15 cm.) of water and was reduced as the lung filled, the lung being at the same time supported either in the same fluid or in physiologic solution of sodium chloride. In one lung the fixative was run into the pulmonary blood vessels while the alveoli were moderately inflated with air injected into the bronchial tree. The lungs were allowed to lie in the fixative for days or even weeks until well hardened. The separate lobes were then cut into slices about half an inch (1 cm.) thick and preserved in 80 per cent alcohol. Lungs with both moderate and full degrees of distention were studied. The fixatives included a dilute solution of formaldehyde U. S. P. (1:10), Bouin's tri-nitrophenol-formaldehyde-tri-chloracetic acid mixture, Orth's fluid and Zenker's solution to which a solution of formaldehyde had been added. Most of the sections were carefully cut and mounted from frozen blocks; in other cases the paraffin method was used.

The pores are best seen in thick, well stained sections permanently preserved in the phase of inflation,[1] because they then may be viewed *en face* in alveolar walls lying parallel with the glass slide. The alveolar sacs of the lungs of older persons are so large that sections of 100 microns or even more may be used to advantage. For the preliminary survey the low and high powers of the Greenough binocular microscope are used, and for the detailed scrutiny the modern binocular monobjective compound microscopes are useful. It was found to be an advantage in each case, particularly for photomicrographic purposes, to prepare a few sections

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From the University of Western Ontario.

Read before the Section on Pathology and Physiology at the Joint Session of the American Medical Association and the Canadian Medical Association, Atlantic City, N. J., June 14, 1935.

1. Macklin, Charles C.: J. Anat. **69**:188, 1935.

by flattening them against the slide prior to staining them. Although most of the field is thus rendered useless, alveolar walls are occasionally seen which present considerable areas lying in one plane and are convenient for study even with the oil immersion lens.

It is evident that alveolar pores do not appear in thin sections as anything but interruptions in the cut alveolar walls, and thus, unless there is some visible material in them and apparently continuous through them, such as the strands of fibrin in cases of pneumonia, they are likely to be overlooked. Hence little attention has been given to them, because thin sections are ordinarily used by the pathologist and histologist in the examination of lung tissue. In ordinary sections the pores are still further obscured on account of the collapsed condition of the lung tissue that is usually studied, for many of the pores are completely closed and all are made smaller.

AGE DISTRIBUTION

Well marked alveolar pores were noted in all the human material studied, which indicates that they are present throughout most of the period of extra-uterine life. There was noted a gradual increase in the number and the size of the pores with the progress of age, thus confirming the reports that have been made by others. This increase in the surface area occupied by the pores seems to be related to the increase with age in the total surface area of the alveolar walls themselves, which occurs coincidentally with the enlargement of the air spaces. The increase in size was observed in all regions of the lung with the advance of years, and in the lungs of old persons the pores were large and conspicuous. Because of this, as well as because of the much greater number of pores, the lungs of the aged present a striking contrast to those of the young, in which the openings occur relatively infrequently and are of comparatively insignificant size.

REGIONAL DISTRIBUTION

Although in the early years of life the pores are fairly uniformly distributed over the lung, they gradually show a predilection for certain definite regions; and in the lungs of persons of middle and later life they are present in largest numbers in the borders and in the apexes of the upper and lower lobes; after that they are most frequently noted in the subpleural regions and in patches in the hilus in the vicinity of the trunks of the large bronchi and blood vessels. Indeed they tend to be somewhat larger and more numerous in the alveolar walls attached to the bronchi and larger blood vessels throughout the lung, and this tendency may possibly be related to the subjection of the walls to greater strain there on account of the functional movements of these tubes.[2] Local

2. Macklin, Charles C.: Physiol. Rev. **9**:1, 1929.

mechanical disadvantages may account for the predominance of the pores in the other regions mentioned.

In a man, aged 40, who was killed instantly in an automobile accident the anterior and lower borders of the intrabronchially fixed lung were found to be riddled with holes, of which figure 2*A* depicts by no means an extreme example. In some cases there was nothing left of the alveolar wall but a flimsy latticework of capillaries and connective tissue fibers. The elastic tissue, though showing some kinking of the finer fibrils, took the stain well and seemed fairly normal. This, to my mind, represented a low grade of emphysema. The pores seemed to be essentially the same as those in other parts of this lung or in other lungs. The subpleural alveolar walls in the region of the apex of the upper lobe were also very porous. The interiors of both lobes showed a comparatively moderate degree of porosity.

In a woman aged 82 the local changes were still more striking. In the borders and the apexes of the upper and lower lobes the openings often occupied much more of the area of the wall than did the surviving capillary mesh, and strands of elastic tissue often crossed the openings. Although some of the pores had regular evenly curved margins, in others the outline was irregular. The capillaries bordering some of them seemed attenuated. There was great variation in size; in some cases the pores were mere pinpricks occupying the ground membrane of Josselyn,[3] while in others they had apparently widened to the limit of the fibrillar meshwork. The condition was more outspokenly emphysematous, although even here the elastic tissue was fairly intact. In the interior of this lung the porosity was of strikingly lower degree; although pores were fairly numerous, there were large areas of the wall which were without them. Here, too, the impression was received that the pores were notable for an increase in size rather than in number. The pores in the interior seemed to be essentially the same as those of the more richly perforated regions.

MORPHOLOGY

The pores were in all essentials like those studied by me [1] in the lungs of the dog, cat, rabbit, guinea-pig and rat, by Josselyn [3] in the rabbit and mink, by Ogawa [4] in a number of animals and in man and by many others. Their rounded or oval outlines and smooth, evenly curved contours did not suggest artificial tears or breaks.[5] In some pores, in which the margin was reeinforced by a ring of elastic tissue or reticulum, there was perhaps room for Josselyn's [3] impression that "in their formation a homogeneous membrane, under some elastic tension, has retracted from

3. Josselyn, L. E.: Anat. Rec. **62**:147, 1935.

4. Ogawa, C.: Am. J. Anat. **27**:333, 1920.

5. Macklin.[1] Josselyn.[3]

a point of rupture to the nearest supporting structures," but in many other cases the pore was but a minute opening in comparatively homogeneous protoplasm without fibrils, and the feeling is that it represented a wasting away, an atrophy, of the ground substance. In some cases, as in that of the 40 year old man, there could be observed in the borders of the lungs, a whole series of pores, ranging from very small to very large ones, and the amount of ground substance bounding each of them was often in inverse ratio to the size of the pore. Thus there is a good basis for the view that the pores arise in many cases, possibly in all, as a result of atrophy, often gradual, of the ground substance within the capillary mesh, beginning at or near the center and enlarging until held by the reenforcing fibers close to the capillary. No evidence has been disclosed

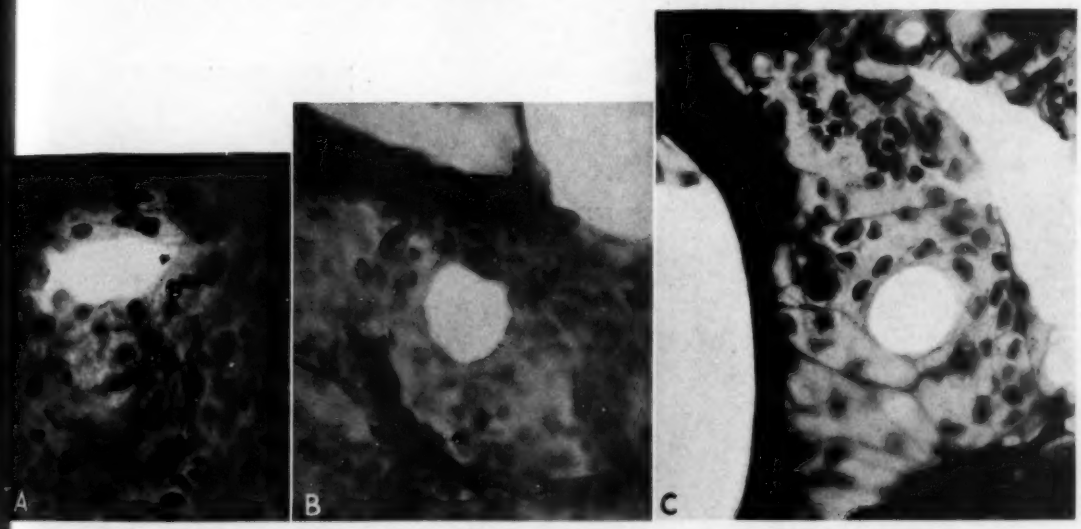

Fig. 1.—*A*, an alveolar pore in the lung of a child aged 2 years and 5 months. The pore is partly closed, as the lung was collapsed. *B*, a pore from an alveolus near the mediastinal surface in the lung of a boy aged 13. The lung was moderately distended with Orth's fluid. *C*, a pore from the lower border of the lung of a woman aged 36. The stained elastic fibers are seen. To the left the dark crescentic band represents the myo-elastic mouth of the alveolus. To the right is an artificial break, which was produced in the preparation of the frozen section (intrabronchial fixation).

indicating a happening like the breaking of a soap film when pricked with a hot needle. It is felt that the origin of the pores is associated with the presence of air in the alveoli.

Representations of alveolar pores of human beings of different ages with the aid of photomicrography are seen in figures 1 and 2. Figure 1*A* shows a section of the collapsed lung of a child of 2 years and 5 months. The pore is partly closed, as shown by the thickened rounded

edges and pointed ends. The alveolar walls in these collapsed specimens are much thicker than those in distended lungs. This is evidently one of the larger pores in this lung. As a rule, pores are rarely seen in the walls of a collapsed lung, even in well stained thick sections and only the largest ones retain any degree of patency, appearing as elongated ovals or slits, much reduced in size. Often the pore is entirely closed and is seen only as a light streak or spot in the wall representing a thinner area. Hence most of the pores are invisible in collapsed lungs. In those that remain partly open,

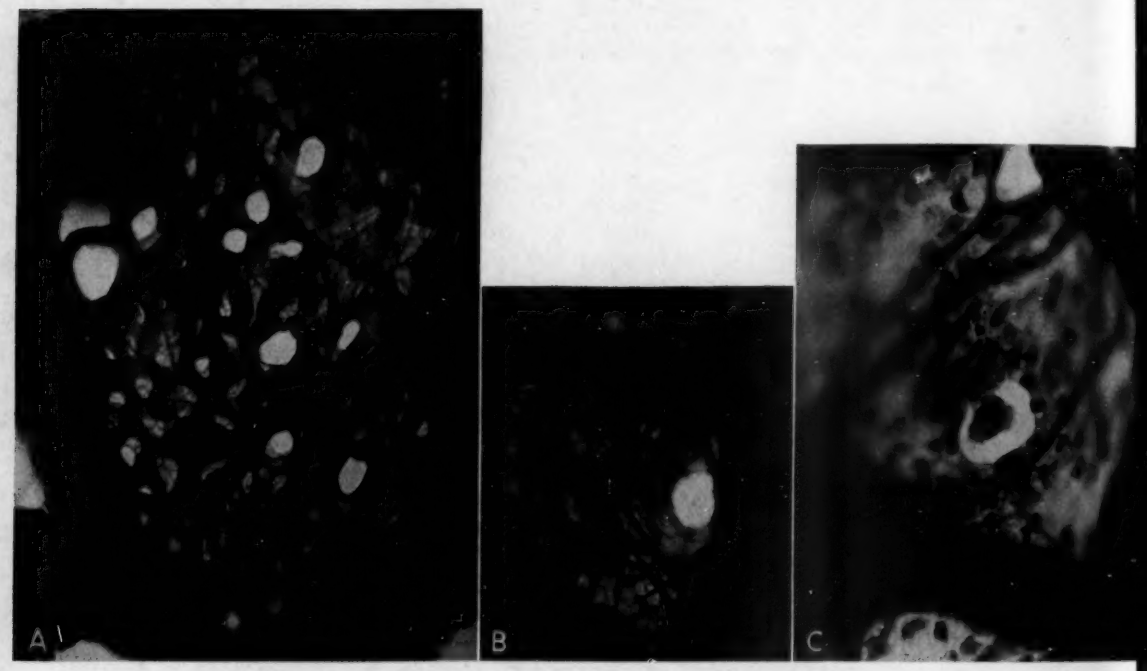

Fig. 2.—*A*, multiple pores from the lower border of the lung of a man aged 40. This was regarded as a case of incipient emphysema. The elastic fibers are stained (intrabronchial fixation). *B*, a pore from the internal tissue of the lung of a woman aged 49 (intrabronchial fixation). *C*, a pore from the interior of the upper lobe of the left lung of a woman aged 49, showing a phagocyte containing dust particles within the pore (intrabronchial fixation). These photomicrographs were taken with a Zeiss 4 mm. apochromatic lens with Zeiss compensating ocular 7×. This, with the extension used, gave a magnification of 370.

the ground membrane is not well seen, and the pore appears to be immediately bounded by the capillary mesh. Yet pores were noted in thick sections in all seven of the human collapsed lungs studied, and this fact makes it easier to believe in the preexistence of these pores in

living tissue, for the factor of mechanical strain in the distention during fixation was eliminated.

It is possible, as has been suggested,[3] that new pores may be formed as a result of intrabronchial fixation—possibly owing to the association of the coagulative effect of the fixation fluid on the ground membrane and the undue stretching of this membrane. In attempting to appraise the results according to the number of pores observed by this method, one should be aware of the fact that pores are then most favorably displayed. It is, to my mind, the method most likely to reveal all the pores, for the thin, curtain-like alveolar walls are stretched and thinned, and the capillary meshes are opened up. Moreover, the equal pressure of fluid on the two sides of the alveolar wall has the effect of smoothing out any inequalities and of pressing all the capillary meshes into the same plane. It is possible, too, that the fluid part of the blood may be pressed out of the capillaries in the thin walls. Certainly the capillaries in such preparations do not bulge into the alveolar spaces as they do in material fixed in situ by the injection of the fixative into the inferior vena cava before the chest is opened. In the last-mentioned cases, because the capillary meshes are often inclined out of the general plane of the wall and also because of the obscuration of the pores by the projecting and swollen capillaries, the number of pores revealed is much less than that when the method of intrabronchial injection is used. One should, then, be on guard against a too ready acceptance of the view that pores can be formed by the intrabronchial injection. In preparations thus made and cut from a frozen block I have seen the nucleated part of a cell broken away from its more outlying protoplasm, but the irregular, often crescentic, outlines of such a break usually betray its artificial origin. The occurrence of such marked regional inequality in the distribution of the pores as that already described in material equally exposed to the effects of the fixative (borders versus interior of a lung, for instance) seems to argue against the view that the pores result from the technic used. The age variation in pores when the technic is uniform points to the same conclusion.

PULMONIC INTERLOBULAR SPREAD

The alveolar pores have recently become of interest because of the suggestion by a group of workers at Yale University, Van Allen, Lindskog and Richter,[6] that these pores may possibly be, at least in part, responsible for the remarkable phenomenon of peripheral spread in the lungs, which they have described. It has been known for some time that the frankly emphysematous lung is permeable to fluids. Indeed, the

6. Van Allen, C. M., and Lindskog, G. E.: Surg., Gynec. & Obst. **53**:16, 1931. Van Allen, C. M.; Lindskog, G. E., and Richter, H. G.: J. Clin. Investigation **10**:559, 1931.

question of the existence of peripheral intercommunications between the respiratory units is a very old one and has made large claims on space in the literature. Van Allen and his colleagues have even suggested a definite physiologic use for what others have looked on as indicative of degenerative change or accident. Their experiments, mainly on the very porous lung of the dog, have led them to postulate a mechanism for a round-about permeation of air from regions still open to the exterior into a region of alveoli the supply air tube of which is blocked, so that these alveoli may, as they have said, "breathe" under these embarrassing circumstances. They have even coined a term for this process—"collateral respiration." Their reports of experiments with the living dog were particularly arresting, for air, in the normal breathing of the anesthetized animal was said to flow continuously for an extended period and in large amount from a secondary bronchus into which an expansile cannula had been tightly fitted and in which a valve prevented any inflow. This air could be entering the territory of the cannulated bronchus only through the frontier of alveolar walls separating it from the neighboring bronchial territory still open to the outside and normally ventilated. When the valve was reversed air was sucked into the cannulated territory with each inspiration, and the fact that no distention was apparent after a prolonged inflow indicated that the air was escaping through the same frontier into the contiguous lung substance. Almost equally striking was the evidence of peripheral spread not only of gases but of fluids and even suspensions of finely particulate matter, which these workers obtained from subdivisions of freshly removed lungs of animals and of man. These substances could be finding their way from the territory of the bronchial subtree directly injected into that of its neighbor only through the alveolar walls, either by simple diffusion or via openings therein, which theoretically might be artificial, natural or pathologic. The possibility that the "pores of Kohn," described many years ago, were implicated occurred to them. In this light these openings, which to me seem to be identical with those that I have described, assume a possible significance.

My attention was attracted to the possibility of the presence of a peripheral thoroughfare in the normal lung for air and fluid while working on a different problem, namely, the morphologic and functional relation of the peribronchial air spaces to the bronchus which they envelop. In injecting a syringeful of hot colored gelatin into a secondary bronchus of a previously warmed dog's lung, with the object of mapping the territory supplied by that bronchus, it was noted that with continuous gentle pressure the gelatin was not restricted to what might be assumed to be the limits of that bronchial subtree into which it was injected but continued, with the application of gentle pressure, to spread far beyond this and even to well out from the mouths of neighboring bronchial subtrees

opening into the main stem, which had been slit open. The flow seemed too rapid to be explained by simple molecular diffusion through intact walls (if such a thing could occur at all); indeed, the phenomenon suggested that anatomic passageways, either preexisting or arising from possible experimental trauma, were being traversed by the gelatin. The observations of Van Allen and his colleagues at once came to mind as providing a starting point for inquiries looking to an explanation of this curious diffusion. The clinical implications, too, seemed worth probing.

I accordingly set out to see these passageways for myself and soon observed them in the lower lobe of the right lung of a cat when the pulmonic capillaries had been filled with berlin blue gelatin injected through the inferior vena cava before the thorax was opened. The lungs had been subsequently fixed while still in situ by allowing Bouin's fluid to seep into the bronchial tree overnight and by subsequent prolonged immersion in a dilute solution of formaldehyde U. S. P. (1:10). A typical pore in this material was shown in my report in the *Transactions of the Royal Society of Canada,*[7] the gelatin-filled capillary forming a conspicuous framework for the opening. The ready disclosure of these pores in other animals and in man followed;[2] indeed, the presence of the pores seemed adequate to explain the phenomenon of spread from lobule to lobule. It appeared that they might be invoked even to give support to the conjectures of Van Allen and his co-workers.

I have carried out a number of experiments in which was manifested what might be called a lobular overflow and which were analogous to those just referred to. When, for instance, a subsidiary bronchial branch of a freshly removed lobe of a dog's lung is tightly cannulated and air is slowly injected at low pressure, the part of the lung belonging to this branch first fills; but, as the Yale workers have pointed out, if the injection is continued slowly and cautiously, the parts adjoining may be seen to be filling, and this process can be made to continue until the entire lobe is filled. I have done this in a number of lobes of dog's lung. The filling thus of the lower one is particularly striking. However, the filling of the contiguous lung substance is possible only under one condition, namely, that its supply bronchi are occluded, for otherwise the air, after inflating the part to a slight degree, issues forth to the exterior through the open bronchi. If the preparation is immersed, many bubbles are seen to leave the open bronchial stems; but if these stems are clamped off the entire lobe fills if the inlet of air is continued. In such a case, after filling the much larger contiguous region, I have withdrawn the plunger of the 100 cc. glass syringe used and so deflated the part into which air was directly injected; and when this was done the adjoining larger region began slowly to deflate with a hissing sound as air emerged from

7. Macklin, Charles C.: Tr. Roy. Soc. Canada, sect. 5, 1934, p. 37.

it into the then collapsed part directly connected with the cannula. Its deflation was slow and became even slower as the volume was reduced, for its only actuating force was the elastic tissue in its walls, and it had access to the outer air only through the frontier separating it from the cannulated part. I have watched this process with interest repeatedly—the filling of the cannulated part first; then, when it has attained a moderate degree of tension, an overflow, as Van Allen and his colleagues have shown, into the adjoining territory; the filling of this when its outlets are blocked; the collapse of the cannulated part when its bronchial outlet is opened, and the seeping back of the air through the intervening frontier from the adjoining part of the lobe, the outlets of which are still closed.

The same phenomenon of lobular overflow may be witnessed when fluids are injected. Using a colored fluid, such as methylene blue in Ringer's solution, cresyl blue in water, janus green in water or Bouin's fixing fluid, I have first seen the filling to a moderate degree of the cannulated fraction of the lobe and then the overflow into the adjoining territory. If the bronchi of the adjoining territory are allowed to remain open the fluid wells out from them, but if they are blocked all this area fills. It is evident that after passing the frontier of the lobule into which it is injected, the fluid or gas enters the bronchial system of the contiguous territory and is distributed through it. The same process may be viewed when hot gelatin is injected.

It was noted that the cannulated territory, when solutions of dyes like methylene blue were injected, took a somewhat darker stain than did the adjoining territory.

When Bouin's fixative was injected into the cannulated part of a lobe of a dog's lung into which methylene blue in Ringer's solution had previously been injected to the extent that the adjoining part had become moderately but not completely filled, it was noted that a fine bluish precipitate was formed, and as the fixative was continuously introduced this accumulated on the frontier of the cannulated part, making it visible. After the portion of lung had been completely filled with the fixative the rubber tubing attached to the cannula was clamped, and the preparation was immersed in a fixative. Sections of the frontier between the cannulated part and its neighboring territory were cut and examined, but no lesions were observed. The fluids passing across this frontier had apparently passed through the pores. The precipitate had drifted to the frontier and had accumulated there as the fluid in which it was being carried filtered through the pores.

A somewhat similar result followed the introduction of a 25 per cent solution of india ink into a fraction of the lower lobe of a dog's lung, but there the flow was not so free and it was felt that this solution of finely particulate matter was not passing through the frontier as readily as had

the molecular solutions. Filtered Bouin's fluid was one of the molecular solutions used, and the same succession of events attended its introduction into the cannulated fraction of the lobe of the dog's lung. The cannulated fraction was the part most intensively stained. Peripheral overflow from it was just as marked as it was with the colored fluids.

OUTLINING THE LOBULAR FRONTIERS

It is evident that if particles of larger size than the pores are mixed with the fluid to be injected into a lobular fraction the particles will remain in the part into which they are directly injected and will tend to accumulate on its periphery as the fluid containing them filters out. This is true no matter what the size of the cannulated territory may be, ranging from a minimum of an "acinus" arising from a respiratory bronchiole (if such could be cannulated) to the largest subdivision of a lobe. Just as a country has its frontier, and within this there are state borders, within each of these county frontiers and so on; so in the lung each lobe has a frontier, and within this are the frontiers of the major lobules served by the main secondary bronchi, within each of these the frontiers of the smaller lobules and so on down to the smallest unit, the pulmonic acinus. And each of these frontier systems can be mapped (at least in the dog) by differential injection—by the use of fluid containing visible particles which cannot pass through the pores. Last year I used the common "bronze powder" of the paint shops suspended in hot gelatin and was able to show that the particles in the lobules of the dog's lung were retained in what appeared to be the territory belonging to the bronchial branch into which the mixture was injected, while the gelatin diffused through beyond the confines of this territory if the injection was continued. Further, the particles became concentrated on the frontier as the fluid gelatin filtered through the pores of the frontier. There was even some concentration of particles at subsidiary frontiers within this large lobule, which demarcated smaller lobules in its interior (fig. 3*A*). I have repeated this injection of bronze powder in hot gelatin and have applied the method to two human lungs, with substantially the same results, though the greater prevalence of connective tissue partitions in the human lung interferes to some extent with diffusion, for these partitions are unperforated. The Yale workers observed that the lungs of pigs and cattle were rich in partitions, which interfered seriously with peripheral spread. These metal particles are easily seen and are carried well by hot gelatin but have the disadvantage of not being sectionable.

I have found stained lycopodium spores useful in mapping the frontiers of cannulated pulmonic fractions. These may be readily stained, for instance, with nile blue sulfate in benzene. It was found that they form a satisfactory suspension in butyl alcohol. This suspension, par-

ticularly when used after the introduction of fixative stopped short of full distention, will clearly mark out the position and extent of the territory of a subsidiary bronchus and its relation to the entire lobe. In figure 4*A* is seen a representation, with the aid of a panchromatic plate, of the use of stained lycopodium spores in mapping a lobular fraction. The darkly stained part represents the territory belonging to the cannulated bronchial branch. In figure 4*B* the lobe has been turned over, and in figure 5 it is shown after having been cut open. In this is well displayed the exact territory belonging to the subbronchus into which the suspension was injected, particularly the frontier of the territory, which is clearly seen on account of the denser stain there, owing to the concentration of stained spores. Particles of calcium carbonate also have been used, with a somewhat similar result; and although most of the substance is retained in the fraction of lung pertaining to the bronchus, some

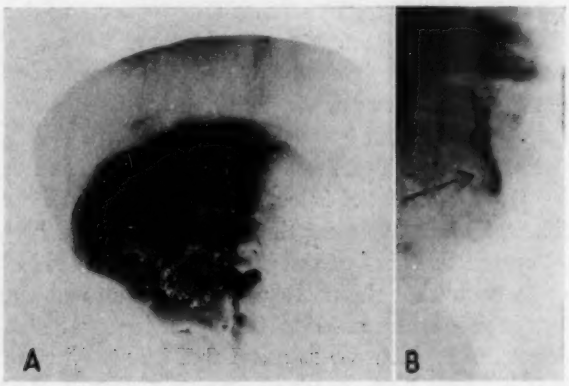

Fig. 3.—*A*, a large lobule of a dog's lung marked out by bronze powder introduced in stained hot gelatin. The spread of gelatin beyond the frontier of the lobule is seen. *B*, roentgenogram of a portion of human lung showing the sharp margin of drifted bronze particles in hot gelatin.

spreads beyond it. This is to be explained by the physical condition of the particles, as revealed by microscopic examination of the suspension, for although a few of the particles are free and some are in small clumps, many are in the form of larger clumps, and it is presumably these clumps which have failed to pass through the strainer of the alveolar wall.

Sections of the frontiers containing lycopodium and calcium carbonate have been cut and stained, and yet no evidences of rupture of the alveolar walls have been noted on microscopic examination. I do not deny that it would be possible with violent methods to create artificial breaks in this frontier, but so far I have not seen any such breaks. It might be possible to create new pores in this way or to enlarge preexisting pores, but on this point I have no evidence.

In the lungs of three persons, aged 39, 48 and 74, respectively, I have obtained evidence of peripheral overflow from the cannulated fraction. In two of these hot gelatin, continuously injected at moderate pressure, returned through the mouths of adjoining secondary bronchi. By means

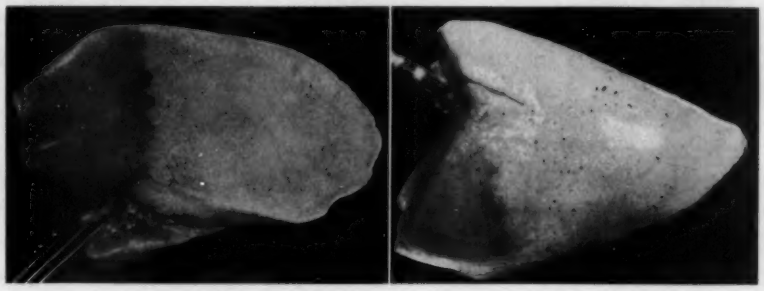

Fig. 4.—*A*, the entire lower lobe of a dog's lung which has been filled by overflow from the cannulated fraction. The area of the latter is marked by the presence of stained lycopodium spores. *B*, reverse side of the same specimen.

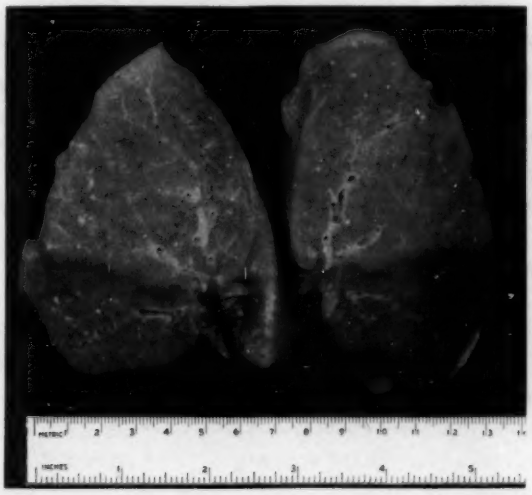

Fig. 5.—Interior of the specimen shown in figure 4.

of this process of lobular overflow the upper lobe of the left lung of the woman aged 74 was entirely filled with colored fluid through a cannula tightly affixed in a subbronchus supplying only a part of this lobe.

It is possible that the method of differential injection with visible large particles, particularly if carried in a subsequently solidifiable menstruum, such as hot gelatin or hot paraffin, will prove a valuable

anatomic assistant in the accurate delimitation of the territory supplied by any given bronchial stem, for instance, the apical bronchus.

COMMENT

All these data on lobular overflow suggest an implication of the pores. To my mind the theory of diffusion through intact alveolar walls is ruled out. Nor do I feel that one needs to postulate the artificial production of openings. Van Allen's experiments on a living dog, already cited, seem to me to obviate that necessity. But, assuming that the pores are to be held accountable for this phenomenon, do they subserve a useful purpose in this connection? Is the system of bronchial distribution perfect in affording equitable accessibility to air to the alveolar walls, or do the pores introduce a final refinement into this distributional mechanism by permitting ready diffusion of air from alveoli with higher pressure to those adjoining with lower air pressure? The relative scarcity of pores in young persons, whose respiratory mechanism is admittedly efficient, gives little encouragement to this surmise. The porosity of highly active lungs, such as those of the dog, possibly might be advanced in support of this surmise. What, too, of the conjecture advanced by Van Allen and his colleagues that localized atelectasis may be interdicted by what I term "lobular overflow" (which I think a more appropriate caption for this phenomenon of peripheral spread than theirs of "collateral respiration"), or of their other suggestion that the broncho-eliminative mechanism is implemented through the accumulation, in any region of lung in which the air tube is blocked by mucus or exudate, of a charge of air, which has seeped in from surrounding still open districts and which may be used in coughing to expel the plug? These are attractive. But if one admits that the pores are essentially a degeneration, one must look on any advantages which they confer as purely fortuitous. All will agree that no beneficent offices should be finally credited to the pores until the related problems have been thoroughly studied in the clinic and in the laboratories of physiology and pathology.

One might ask: Are there two types of pores: (*a*) those observed in perfectly normal lungs of young persons and animals and (*b*) those observed in emphysema in both man and animals? Josselyn [3] has just reported the observation of extremely porous alveolar walls in an old rabbit, the description of which corresponds with mine of the borders and apexes of the lungs of middle-aged and old persons. I must confess that up to the present I have been unable to distinguish any essential difference between the two types. Of course, the frankly emphysematous lung tissue, with degenerate elastic and reticular fibers, widely dilated spaces and ragged openings, is readily recognized, but the borderland

between this and the normal alveolar wall with only one or two small pores is not at all well defined. I have observed in human lungs a few examples of what I call hourglass pores in the narrowed interval between the funnel-shaped ends of adjoining alveoli, but these may be merely variants of the other pores, occurring in small alveolar walls—so small, in fact, that the pore occupies the entire wall and incidentally acquires a stouter boundary. If they do actually facilitate the equalization of alveolar air pressure and are not present at birth (as is the prevalent view), it might be argued that they mark spots where the wall has broken through because of persistently greater pressure in one alveolus than in its neighbor; but there is nothing to support this theory, and the presence of pores in low interalveolar partitions between alveoli which are in open communication above the partition, being merely outpocketings from the same alveolar sac (and such alveoli are fairly numerous), does not favor the ascription of any function in promoting equality of alveolar air pressure. On the whole, the view that they are essentially sharply localized degenerations of the ground substance of the alveolar wall (the *trous d'usure* of the French authors) appeals to me most strongly at the moment. Man begins to die from the instant that he is conceived, and these pores may perhaps be interpreted as early evidences of limited and minute senile change, occurring, paradoxically, even in the young. The etiologic relation of the pores to the fenestrae in emphysema, which interested Letulle [8] and many others, should be further studied. If the pores are regarded as evidences of emphysema, incipient though it may be, then emphysema in this broader sense is almost universal in the mammals and is present in the young as well as in the old.

Are the pores harmful in allowing diffusion of dust or bacteria? Do they spread disease? The only observation bearing at all on this question that I have made, except the ready spread of finely particulate matter through them, is that pigmented phagocytes are not infrequently observed within the pores, apparently passing through them. Brodersen [9] gave a figure of such a phagocyte passing through the alveolar wall. I have noted the spread of carbon particles by way of the emigrating phagocytes in areas surrounding foci of injected india ink in the lungs of cats. It is possible that phagocytes carrying living bacteria, such as Bacillus tuberculosis, might so spread the disease, though it must be admitted that about tuberculous and similar foci there are inflammatory reactions which close the pores, even if the "physiologic shutdown" which has been described by Van Allen and his colleagues does not do so. Possibly the close inspection of admittedly emphysematous lungs with

8. Letulle, Maurice: Arch. méd.-chir. de l'app. respir. **3**:89, 1928.
9. Brodersen, J.: Ztschr. f. mikr.-anat. Forsch. **32**:73, 1933.

these queries in mind would reveal pertinent information, for such lungs are obviously rich in pores. The possibility of the spread of the fluid of pulmonic edema through the pores also should be kept in mind. Whatever the origin of these pores may be, their presence bears on the problem of the mechanics of external respiration.

Case Reports

MORBID ANATOMIC CHANGES IN CASES OF BRUCELLA INFECTION IN MAN

With Report of a Necropsy

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Brucella infection in man is recognized with increasing frequency, and many papers are appearing on the subject. Few papers, however, have dealt with the morbid anatomic changes in man, and these few are not in agreement. In this paper a critical review of the reported morbid anatomic observations is made, and the results of an additional necropsy are described.

REVIEW OF THE LITERATURE

In 1887 Bruce [1] established Micrococcus melitensis as the etiologic agent in Malta fever. Ten years later, Bang [2] discovered the bacillus of contagious abortion in cattle, and Traum [3] observed a similar organism in cases of contagious abortion in swine. Evans [4] demonstrated that Bacillus abortus and M. melitensis have similar cultural, morphologic and serologic characteristics. Keefer [5] reported the first proved case of human infection with the bacillus of contagious abortion. Hallman and his associates [6] have studied and described in detail the morbid anatomic changes produced in animals by Brucella infection.

The earliest report on the morbid anatomic changes in man was made by Hughes,[7] who described the observations in sixty-two necropsies. Although microscopic studies were made in only two cases, it seems certain that the lesions were the result of infection with Brucella melitensis. In the acute stages the author observed congestion of the brain, enlargement of the spleen and dark red or red-black, patchy areas of pneumonia in the lungs, and in three instances he noted vegetations on the mitral valves which he believed to be of previous origin.

From the Departments of Pathology and Pediatrics, the Duke University School of Medicine and the Duke Hospital.

1. Bruce, D.: Practitioner **39**:161, 1887.

2. Bang, B.: J. Comp. Path. & Therap. **10**:125, 1897.

3. Traum, J.: Ann. Rep., U. S. Dept. Agric., 1918, vol. 86.

4. Evans, Alice C.: J. Infect. Dis. **22**:580, 1918.

5. Keefer, Chester C.: Bull. Johns Hopkins Hosp. **35**:6, 1924.

6. Hallman, E. T.; Sholl, L. B., and Delez, A. L.: Michigan State College, Agric. Exper. Stat., Tech. Bull. 93, 1928.

7. Hughes, M. Louis: Mediterranean, Malta or Undulant Fever, New York, The Macmillan Company, 1897, p. 167.

The gastro-intestinal tract was congested throughout, but most markedly in the large intestine. Here the mucosa was edematous, and in some instances the reaction was inflammatory. In cases of chronic infection the spleen was slightly enlarged. Cardiac failure occurred in three cases, and pericardial effusion and mitral lesion in one instance. Hewlett [8] studied microscopic preparations in one case and noted almost completely organized vegetations and round cell infiltration of the mitral valve. The alveoli and alveolar walls of the lungs were infiltrated with large "catarrhal cells" and contained shreds of fibrin. The liver showed only cloudy swelling. An increase in the number of lymphoid cells in Peyer's patches was observed. Bruce [9] noted proliferation and swelling of the "endothelial plates" of Peyer's patches. In the mesenteric nodes there were proliferation of the lymphoid tissue and of endothelial plates and almost complete obliteration of the reticulum. In the spleen the malpighian bodies were enlarged, apparently owing to the increase in the number of lymphoid cells; the endothelial plates of the marginal sinuses were swollen, and a few micrococci were noted. There was tubular nephritis. Kennedy [10] demonstrated Brucella organisms in the spleen, liver, kidneys, lymph nodes, blood, urine, pericardial fluid and bile of patients dying of Malta fever. The lymph nodes contained a fluid which had the gross appearance of pus.

Eyre [11] summarized the pathologic observations made prior to 1908. The summary is valuable because of the author's extensive experience with the disease. He noted that the endothelium of the blood vessels was damaged so that the blood easily passed through. Localized extravasations of blood frequently were noted in the subperitoneal connective tissue. The pericardial fluid usually was increased in amount and contained M. melitensis. Small areas of congestion commonly were observed throughout the intestines, occasionally associated with extravasation of blood. In the cases of chronic infection with diarrhea, the superficial mucosa sometimes was sloughed. There was a slight increase in the amount of fat in the liver. The spleen always was increased in weight and usually was soft and friable. The kidneys generally were not involved, but they sometimes resembled the "large white kidney" of Bright's disease. The mesenteric nodes were often enlarged (from 10 to 12 mm. in diameter), and many contained semifluid pulp from which M. melitensis was obtained. The bone marrow was of normal appearance but contained the organism. The brain and spinal cord usually were normal, but the amount of cerebrospinal fluid sometimes was increased. The chief microscopic changes were: increase in the number of the lymphoid elements of the spleen; numerous nucleated red cells, giant cells, mononuclear cells and lymphoid cells in the bone marrow and decrease in the number of myeloid cells. Large "endothelial cells" containing phagocytosed red

8. Hewlett, cited by Hughes,[7] p. 173.

9. Bruce, D., cited by Hughes,[7] p. 173.

10. Kennedy, J. Crawford: Reports of the Commission for the Investigation of Mediterranean Fever, London, Harrison & Sons, 1906, pt. 4, p. 92.

11. Eyre, J. W. W.: Lancet **1**:1747, 1908.

cells were observed in the spleen, liver and kidneys. Carbone,[12] Tomaselli [13] and Pepere [14] reported anatomic observations in cases of Malta fever, but we believe that most of the lesions which they described were postmortem changes. However, the three authors agreed on the presence of red cells in large numbers in macrophages of the spleen and lymph nodes.

Mettier and Kerr [15] reported an instance of infection with a caprine strain in a 57 year old animal worker. Agglutination tests for Brucella gave positive results in titers of from 1 : 320 to 1 : 640. Cholecystectomy was done during the course of the disease, and sections of the liver were removed. They showed granulomas composed of epithelioid cells, lymphocytes, fibroblasts, a few giant cells and eosinophils and numerous gram-positive rods. A caprine strain of Br. melitensis was cultured from the tissues.

De La Chapelle [16] reported a case in an Italian laborer, aged 38, who contracted the disease from drinking goat's milk. The disease ran a course similar to that of subacute bacterial endocarditis and terminated in death nine months after the onset. Br. melitensis was recovered from the blood stream on two occasions. The red cell counts were 3,930,000 and 3,600,000, with 48 and 55 per cent hemoglobin, respectively. The white cell counts were 3,350 and 1,800, with 69 and 66 per cent polymorphonuclear cells, respectively. At necropsy petechial hemorrhages were noted on the right foot and in the kidney. Beneath the peritoneum was a clot of blood which weighed 450 Gm. No source of this blood was determined. The heart was not enlarged. The liver, spleen and lymph nodes were enlarged and swollen. Microscopically, the liver showed marked degeneration about the central veins and focal areas of fat. In the spleen were scattered areas of necrosis. The microscopic appearance of the lymph nodes was not studied. Red cells were noted in the glomerular spaces and also in the tubules of the kidney, but no bacteria were seen.

In the aforementioned cases the infection was caused by the caprine form of Brucella. In most of the cases reported in recent years the disease has been due to bovine and porcine strains. Matzdorff [17] collected nine cases from the literature and added one of his own. In all except the case he reported, the disease was diagnosed by the finding of agglutinins in the blood serum. Four of the cases collected by Matzdorff may be discarded, as the patients died of other diseases and no morbid anatomic changes were observed which might be attributed to Brucella infection. In the remaining five cases lesions occurred which were somewhat similar to those of Brucella infection in animals. The case of Katsch and Guillery,[18] however, cannot be included

12. Carbone, T.: Arch. per le sc. med. **28**:273, 1904.

13. Tomaselli, A.: Policlinico (sez. med.) **18**:132, 1911.

14. Pepere, A.: Pathologica **2**:295, 1910.

15. Mettier, Stacy R., and Kerr, William J.: Arch. Int. Med. **54**:702, 1934.

16. De La Chapelle, C. E.: Am. Heart J. **4**:732, 1923-1924.

17. Matzdorff, F.: Virchows Arch. f. path. Anat. **290**:47, 1933.

18. Katsch and Guillery, cited by Wohlwill.[20]

because of insufficient data, and that of Löffler and von Albertini,[19] owing to the uncertainty of the diagnosis.

Wohlwill [20] described a case in a woman, aged 67, who had had diabetes for six years. The serum agglutinated Brucella abortus in dilutions of 1:3,200. Bilateral pleurisy developed four weeks after the onset of fever, and death from pulmonary embolus occurred ten days later. At necropsy an embolus from the femoral vein was seen to plug the main branch of the pulmonary artery. The spleen and lymph nodes were enlarged, and there was slight inflammatory reaction in the capsule of the spleen. Microscopically, tubercle-like masses were observed in the spleen, lymph nodes and bone marrow. In the liver there were areas of necrosis. Guinea-pigs were inoculated with blood from the heart, bile and material taken from the liver, spleen and bone marrow. No agglutinins were found in the serum of the animals after eight weeks, and no changes were observed at necropsy. However, the case seems to us a true instance of Brucella infection.

Rössle [21] reported the results of a study of an axillary lymph node taken from a butcher, aged 27, who had been infected through a wound of the hand. The agglutination titers as determined later were between 1:38,000 and 1:12,520. This would seem to make the diagnosis of Brucella infection certain. The lymph nodes were swollen and contained masses of "reticulocytes" which were thought to be similar to the granulomas described in animals.

Gregerson and Lund [22] cited the case of a woman, aged 53, whose serum agglutinated Brucella in dilutions of 1:400. She had a temperature of 41.5 C. (106.7 F.) for ten days. At necropsy the spleen weighed 605 Gm. and showed congestion; the malpighian corpuscles were small. In a vein was an organized thrombus. In the splenic pulp were nodules composed of fibroblasts of a simple type and a few lymphocytes, but no epithelial cells. The other organs showed nothing remarkable.

Matzdorff's [17] case was that of a teacher, aged 37, with aortic stenosis the agglutination titer of whose serum for Br. abortus was 1:3,200. Blood cultures were not made. At necropsy the following conditions were noted: aortic endocarditis of long standing with a fresh reaction on the wall of the heart, parenchymatous degeneration of the heart muscle, anemic infarct of the right kidney, hemorrhagic cystitis, gastritis, enterocolitis, hyperplasia of the hilar lymph nodes, acute splenic tumor, passive congestion of the liver and acute glomerular nephritis. There was no hyperplasia of the reticulo-endothelial system, but considerable phagocytosis of red cells, blood pigment, fat and the nuclei of disintegrated cells was noted. The capsules of the lymph nodes around the hilus were infiltrated with lymphocytes. There were red cells as well as other cells in the sinuses of the nodes. The bone marrow showed no change. Emulsions of material taken from the aortic lesion and the spleen produced the disease when injected into guinea-pigs.

19. Löffler, W., and von Albertini, A.: Krankheitsforschung **8**:1, 1930.

20. Wohlwill, F.: Virchows Arch. f. path. Anat. **286**:141, 1932.

21. Rössle, R.: München. med. Wchnschr. **80**:5, 1933.

22. Gregerson, F., and Lund, T. M.: Hospitalstid. **74**:349, 1931.

Besides the instances cited by Matzdorff,[17] the following cases are reported in the English literature:

Hansmann and Schenken [23] reported an instance in a white man, aged 24, a printer, whose condition was first diagnosed as encephalitis associated with low grade meningitis. Later a porcine strain of Br. melitensis was isolated from the spinal fluid. Death occurred thirteen months after the onset of symptoms. The organism recovered from the spinal fluid produced the disease when injected into a guinea-pig. The patient's serum agglutinated strains of Brucella in dilutions of from 1:40 to 1:160. The agglutination titer of the spinal fluid was 1:10. At necropsy the spleen weighed 175 Gm., and three small hemorrhages were seen on the pericardium. Liquid and clotted blood was present in the subarachnoid space and filled the cisterna magna, the fourth ventricle, the aqueduct of Sylvius and the third ventricle. An aneurysm of the dorsal portion of the proximal part of the basilar artery was observed. Histologic examination showed considerable amounts of hemosiderin in the lungs and a few small areas of focal necrosis in the liver. The pia and arachnoid were thickened, owing to inflammatory cells and to proliferation of connective tissue. Most of the vessels of the meninges showed a thickened adventitia, which was heavily infiltrated with cells. Many blood vessels in the brain were surrounded with collars of lymphocytes. Inflammatory cells also were present in the perineurium of the nerve roots.

Hardy, Jordan, Borts and Hardy [24] reported the case of a housewife, aged 57, who had a febrile illness for ten months. Two months before death, Br. abortus was agglutinated by the serum in dilutions of 1:640 and 1:1,280. No cultures of the blood were made. A partial necropsy showed "chronic interstitial pancreatitis, cholecystitis, fatty infiltration and passive congestion of the liver and fragmentary myocardial degeneration." A moderate number of mononuclear cells were present in the sinuses of the spleen. The lymph nodes and bone marrow were not studied.

A second case reported [24] was that of a man, aged 21, a packing-house employee, in whose blood agglutinins were present in a titer of 1:2,060. Death from cardiac failure occurred three months after the onset. Necropsy revealed a hypertrophied heart weighing 597 Gm. An abscess in the anterior portion of the mediastinum containing blood and pus had eroded through the wall of the aorta and destroyed the anterior cusp of the aortic valve. The liver was of the nutmeg type, and the cells around the central veins were necrotic. The spleen was enlarged, and few reticular cells were swollen. Several lymph nodes showed reticulo-endothelial hyperplasia and phagocytosis of red cells.

Amoss [25] described a case of Brucella infection associated with tuberculosis in a white woman, aged 28. Brucella was recovered from the stools and the blood, and agglutinins were present in the blood.

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23. Hansmann, S. H., and Schenken, J. R.: Am. J. Path. **8**:435, 1932.

24. Hardy, A. V.; Jordan, C. F.; Borts, I. H., and Hardy, G. C.: Undulant Fever, with Special Reference to Study of Brucella Infection in Iowa, Nat. Inst. Health Bull. **158**:1931.

25. Amoss, H. L.: Internat. Clin. **4**:93, 1931.

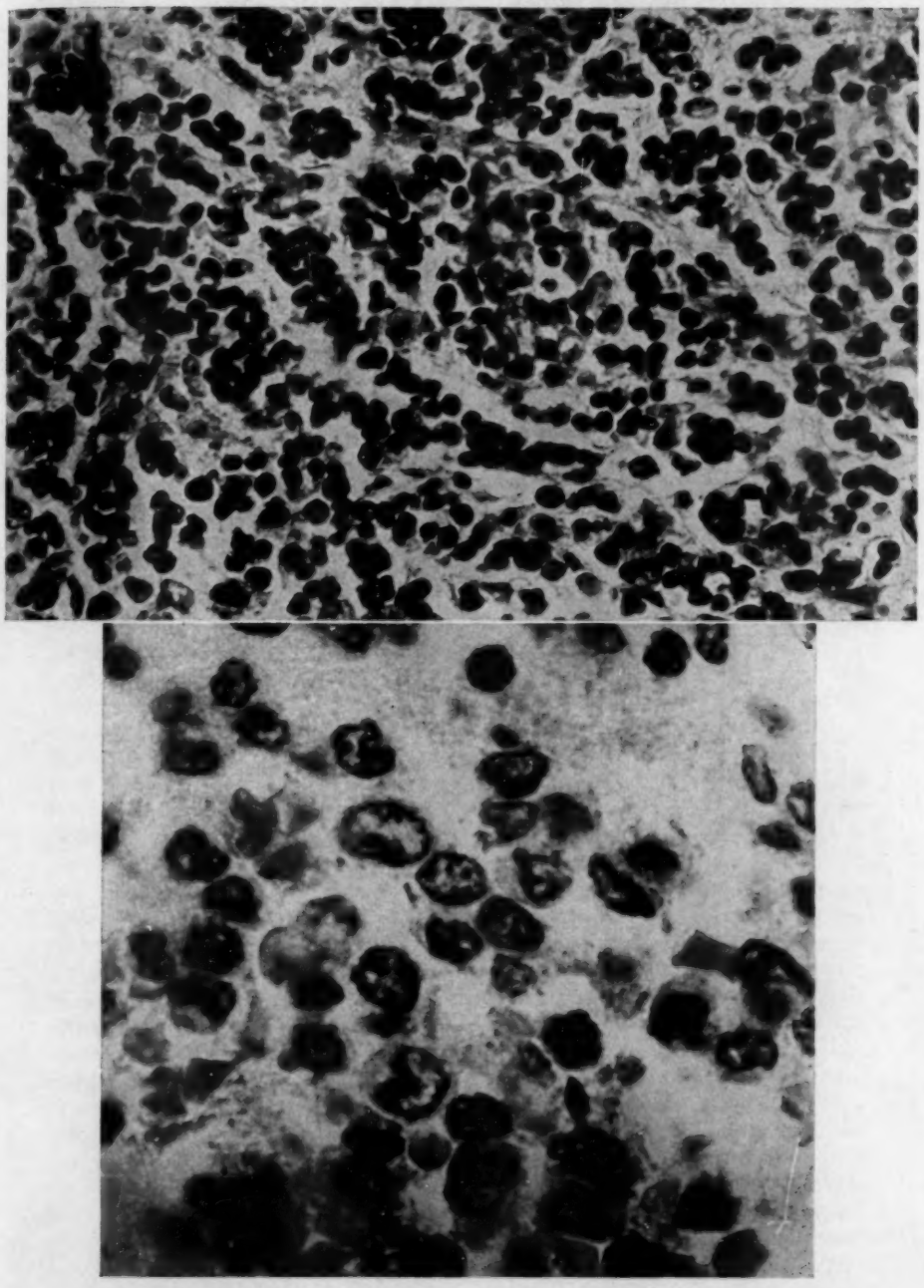
Because of recurrent twinges of pain in the right lower quadrant, appendectomy was performed. The appendix was enlarged and fibrous. Many white papules resembling tubercles were seen on the peritoneum. Histologically, these lesions resembled those of tuberculosis, although there was less fibrous tissue than usual. Neither the tubercle bacillus nor Brucella was observed in the appendix, but both organisms were noted in the right fallopian tube. In addition, Amoss mentioned two cases, in both of which the gallbladder was removed during the course of Brucella infection. Histologic preparations of the gallbladders showed only fibrosis.

REPORT OF A CASE

History.—A white boy, 4 years of age, was admitted to the Duke Hospital in April 1933, with the complaint of intermittent fever of fifteen months' duration. The illness began with attacks of headache, accompanied by pain in the abdomen. Vomiting was said to relieve the symptoms. Six months later the child had dysentery, and following this illness intermittent fever was noted. The febrile periods lasted from ten to fourteen days, with the temperature reaching 39 C. (102.2 F.) daily, and alternated with afebrile periods of from seven to ten days. When the patient was admitted to the hospital in the fifteenth month of his illness, the physical findings were slight malnutrition, pallor and generalized weakness. The liver could be palpated about 4 cm. below the costal margin. Treatment consisted of repeated subcutaneous injections of heat-killed and formaldehydized autogenous and stock Brucella vaccines and, finally, in the month before death, of three treatments by production of artificial fever, the rectal temperature being elevated to 41.3 C. (106.3 F.) for five hours on each occasion. Thirteen blood transfusions were given, six during the last month of life. These measures resulted in no permanent improvement. The patient died ten months after admission to the hospital, with aplastic anemia and massive cervical adenitis and cellulitis which necessitated tracheotomy twenty-four hours before death. The cervical lymph nodes had been enlarged for four months.

Laboratory Data.—On admission to the hospital the red blood cell count was 3,840,000, the hemoglobin content 9.5 Gm. per hundred cubic centimeters of blood and the white blood cell count 4,000, with 44 per cent polymorphonuclears, 5 per cent large lymphocytes, 47 per cent small lymphocytes and 4 per cent monocytes. Urinalysis and the Wassermann and tuberculin tests gave normal results. The blood serum agglutinated Bacillus dysenteriae (Shiga) in a dilution of 1:640, but there were no agglutinins for Brucella, typhoid or paratyphoid organisms. The cutaneous test for Brucella was negative. However, a bovine variety of B. melitensis was grown in cultures of the blood and of the contents of the duodenum soon after the patient's admission to the hospital. The white blood cell count averaged about 2,000 during the illness, with a preponderance of lymphocytes. The blood picture as the illness progressed was that of aplastic anemia, with a rapidly decreasing red cell count, a decreased number of white cells and marked reduction in the number of platelets.

Observations at Necropsy (One Hour after Death).—The body was well nourished. There was a recent tracheotomy wound in the midline of the neck. The lymph nodes of the neck and the anterior portion of the mediastinum were swollen, while those of the axillary and inguinal regions and of the abdominal cavity were not enlarged. There were fibrinous pleurisy and areas of atelectasis. The remaining organs of the body other than the spleen, which was slightly enlarged, showed no gross changes. Permission to examine the brain was not obtained.



Photomicrographs (× 550 and × 1,800, respectively) of the marrow of the femur. Mitotic figures and replacement of the normal marrow cells by atypical mononuclear cells are evident.

The tissues were fixed in Zenker's fluid (Helly modification) and a dilute solution of formaldehyde U. S. P. (1:10). Sections were stained with hematoxylin and eosin by the Giemsa method, with sudan IV for fat, by both the MacCallum and the Brown and Brenn method for bacteria and for hemosiderin.

One of the most interesting features in this case was the presence in many of the organs of peculiar mononuclear cells. These cells had deeply staining nuclei and scanty, pale-staining cytoplasm. They rather closely resembled lymphocytes. Oxidase stains could not be made, but sections stained by the Giemsa method showed no granules. We were not able to classify these cells definitely; they may be premyelocytes, lymphocytes or monocytes; we believe that they are lymphocytes.

On the pleura were masses of fibrin and amorphous pink-staining material containing numerous cells. There was proliferation of the pleural endothelium, and infiltration with round cells extended into the interstitial tissue of the lungs. No mitotic figures were present. In the fibrin over the pleura were a large number of cocci in chains, which proved on culture to be staphylococci. A few short gram-negative rods, which perhaps were Brucella, were stained also. It is interesting that, despite the presence of the staphylococci, few polymorphonuclear cells were present. The alveoli in many places contained red cells and a few polymorphonuclear cells. In regions adjacent to the pleural reaction there was atelectasis. The splenic pulp contained a large number of phagocytic cells which were filled with hemosiderin. The malphigian corpuscles were relatively small and inactive, and some contained hemorrhages. The cells of the liver were uniformly swollen, and a few were stained more deeply with the acid stain than were the surrounding cells. The Kupffer cells were not increased in number but were filled with hemosiderin. All the hepatic cells contained small droplets of fat.

There were no changes of interest in the thyroid, but the adjacent tissues contained numerous gram-positive cocci. These cocci were probably of the same strain of organisms as those which were cultured from the lungs. As they were seen adjacent to the tracheotomy wound, it is thought that they gained entrance at that point. This was borne out by the fact that the polymorphonuclear cells were more numerous there than elsewhere. Besides the polymorphonuclear cells there were also a number of the peculiar mononuclear cells already described. The peripheral sinuses of lymph nodes from the hilus of the lungs and from the mediastinum were filled with mononuclear cells. The lymph nodes of the mesentery presented a different picture, for there the lymph follicles were missing and the peripheral sinuses contained red cells, many of which had been phagocytosed by macrophages. In some of the mesenteric nodes there was a slight increase in the amount of reticulum, but this was not pronounced. The remainder of the node was infiltrated with the mononuclear cells. The tonsils presented the same picture as that of the lymph nodes. Bone marrow was studied from the shaft of the femur and from a vertebra and a rib. In the sections taken from the femur the normal cells were completely replaced by mononuclear forms. In one section there was necrosis, but no hemorrhages were seen. The sections taken from the rib and the vertebra showed essentially the same picture except that there were a few small hemorrhages. There was marked proliferation of the periosteum of the ribs. Some of these cells were periosteal, and others were the mononuclear cells previously described.

Numerous focal areas of necrosis were seen in the convoluted tubules of the kidneys, and a few glomeruli were slightly swollen. No fat was present in the kidneys. Throughout the interstitial tissue of the testes and especially in the

epididymis were large numbers of mononuclear cells. The heart, gallbladder, adrenals and intestines showed no changes.

Bacteriologic Report.—Cultures of the blood from the heart and of the bile obtained from the gallbladder were sterile, but Brucella organisms were obtained in pure culture from the liver and spleen. Staphylococcus aureus of the hemolytic type was cultured from the lungs.

Anatomic Diagnosis.—The anatomic diagnosis was: Brucella infection, extensive destruction of the blood with deposits of hemosiderin in the liver, spleen and kidneys; cloudy swelling of the hepatic cells and fatty change in the liver; necrosis of the convoluted tubules of the kidney; fibrinous and proliferative pleuritis; pleural effusion; edema of the glottis; laryngitis; tracheitis; tracheotomy wound; terminal staphylococcic infection, and acute mediastinitis.

COMMENT

One cannot ascribe the lesions in this case to Brucella infection until the part played by the staphylococci is determined. Although it is difficult to determine the time of onset of the infection with this organism, the clinical history indicates that it occurred in the last few days of the disease and played only a terminal part in the death of the child.

Certain lesions frequently are observed in cases of Brucella infection in man:

Anemia.—Anemia due to Brucella infection is the result of two factors, and in this case a third may be added. Most writers have noted that hemorrhages occur in the lymph nodes, the intestines and other organs during the course of the disease. De La Chapelle [16] reported an instance of a large retroperitoneal hemorrhage. These hemorrhages, however, do not account for much of the anemia. The true source of the anemia seems to be destruction of the red cells in the blood stream. In the present case, in addition to hemorrhages, the body had lost its ability to form red cells, the bone marrow being replaced by the peculiar mononuclear cells previously described.

The changes in the spleen and liver are the result of the extensive destruction of the blood cells and are similar to the changes produced in any disease by the breaking down of blood cells. The numerous transfusions probably account for most of the pigment, although some may have been the result of the destruction of the patient's red cells due to the Brucella infection. Since the work of Bruce it has been established that this destruction of cells occurs.

Valvular Endocarditis.—In the cases of Hughes,[7] De La Chapelle [20] and Matzdorff,[15] there was evidence that vegetative lesions on the valves of the heart may occur in Brucella infection in man.

Phlebitis.—In the case of Gregerson and Lund [22] it was shown that phlebitis may occur.

Changes in the Kidney.—In cases in which microscopic studies of the kidneys were made the common lesion was cloudy swelling, and there was rarely necrosis of the convoluted tubules. Earlier reports mentioned gross changes diagnosed as glomerular nephritis. It appears that Brucella possibly may produce glomerular nephritis, though De La Chapelle [20] has given the only good evidence of such lesions.

Involvement of the Joints.—Simpson [26] reported severe symptoms of involvement of the joints in seven of sixty-three cases of undulant fever. In three cases the symptoms were so severe that an initial diagnosis of acute rheumatic fever was made. Many authors have reported symptoms of spondylitis and hydrarthrosis.

Meningitis.—Hansmann and Schenken [23] gave the only report of the morbid anatomic changes in a case of Brucella infection involving the brain. The lesion reported by these authors was mainly the result of hemorrhage from a mycotic aneurysm. There seems, however, little doubt that some of the meningeal reaction was due to Brucella. Besides their case, Hansmann and Schenken cited others in which irritation of the meninges due to Brucella was shown clinically. Recently, Rutherford [27] reported three cases and cited five more from the literature in which papilledema occurred in association with Brucella infection.

Reactions of the Reticulo-Endothelial System.—Amoss [25] has characterized Brucella as belonging to a group of organisms which stimulate the production of lymphocytes, in contradistinction to the streptococcus and other groups of bacteria, which stimulate the production of polymorphonuclear cells or the myeloid series. He stated that while this response is not always present it is frequently observed.

The work of Hallman and his associates [6] with animals bore out this concept. They expressed the belief that the fundamental lesion consists essentially of endothelial cells, with a variable number of lymphocytes and fibroblasts. They observed that giant cells are present at times but not so frequently as in the specific tubercles. They also pointed out that necrosis may occur and that these necrotic areas may become invaded by polymorphonuclear cells. The types of cells vary considerably; in some instances the lesions are composed entirely of endothelial cells while in others there are large numbers of lymphocytes and fibroblasts. These observations are identical with the morbid anatomic changes in man. In the cases of Mettier and Kerr [15] the lesions might easily have been mistaken for tuberculosis; in the case of Rössle [21] only masses of endothelial cells were shown, and the reports of Hardy and his co-workers [24] furnished evidence of more generalized reticulo-endothelial hyperplasia. The case reported in this paper shows evidence of a peculiar proliferation of mononuclear cells which we believe are similar to the cells described by Hallman [6] in animals. In addition to the more chronic forms of reaction the organism may act in a manner similar to Streptococcus viridans in subacute bacterial endocarditis, as indicated in the case reported by De La Chapelle.[16]

SUMMARY

The literature on the morbid anatomic changes in Brucella infection is reviewed, and an additional case is reported. It is pointed out that the reaction of the host may vary from a lesion which simulates tuberculosis to one of only slight stimulation of the endothelial system, or there may be no lesions at all.

26. Simpson, W. M., and Frazier, Eunice: J. A. M. A. **93**:1958, 1929.

27. Rutherford, C. W.: J. A. M. A. **104**:1490, 1935.

Laboratory Methods and Technical Notes

AN ECONOMICAL METHOD OF DEMONSTRATING THIN SECTIONS OF TISSUE

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An ideal museum jar for demonstrating pathologic specimens can be constructed in the laboratory at little cost. It should be made as thin as possible to allow for easy handling, transportation and storage and to demonstrate the widest cross-section area of the specimen, regardless of its size. It should not have bulk or excessive weight and should be leak-proof and durable despite any rough handling it may receive.

In 1932 Davis and Amolsch [1] described a technic for constructing a thin museum cell which embodies all these desirable features. Their museum cell measured 5 by 7 by ¼ inch (12.7 by 17.78 by 0.64 cm.). Our method is a modification of their technic in that it further simplifies the procedure and permits the construction of larger museum cells. One of the largest cells in our collection measures 15 by 15 by ½ inch (38 by 38 by 1.2 cm.) and encloses the cerebral hemisphere of a hydrocephalic brain (fig. 1). This is also one of our oldest mountings and has been preserved for three years without leakage or discoloration.

CONSTRUCTION OF THE CELL

Materials Required.—The materials required are shown in figure 2.

1. Glass Plates: These plates are made of ordinary window glass of ⅛ inch (0.3 cm.) thickness. Two pieces of identical length and width are cut for each cell. The size of the glass depends on the size of the tissue and can be gaged by allowing a 1½ inch (4 cm.) border between the tissue and the periphery of the glass.

2. Brass strip (obtained from the Whitehead Metal Manufacturing Corporation, New York): The strip as purchased measures 12 feet long by ½ by 1/16 inch (366 by 1.2 by 0.16 cm.) or 12 feet by ¼ by 1/16 inch. Either the half-inch or the quarter-inch width can be used, depending on the thickness of the tissue. The strip or a portion thereof should be cleaned and polished before the cell is constructed. The length of the strip is cut for three sides only, the fourth or closing side being added separately. The length should measure 2¼ inches (5.72 cm.) less than three sides of the glass, so that when bent into three sides of a rectangle each side of the brass fame is ¾ inch (1.9 cm.) less than the corresponding glass side and the whole makes a frame ⅜ inch (0.96 cm.) smaller in all measurements than the glass rectangle.

Before the strip is bent, the ends of the strip are beveled off with a file, and nicks are made along the length of the strip at the two points of bending. The nick, which is made by filing the strip two thirds through, produces a neat right-

From the Department of Pathology, Morrisania City Hospital.

1. Davis, J. E., and Amolsch, A. L.: Arch. Path. **14**:372, 1932.

angle bend. For example: A 10 by 5 inch (25.4 by 12.7 cm.) museum cell requires a brass strip 22¾ inches (56.8 cm.) long, which should be nicked 9¼ inches (23.5 cm.) and 13½ inches (34.3 cm.) from either end.

3. Refined Trinidad Lake Asphalt (Genasco Brand, The Barber Asphalt Co., Philadelphia): The asphalt is slowly heated over a bunsen burner in a large metal spoon to which a long wooden handle is attached. The mouth of the spoon is narrowed to permit the pouring of a thin stream of the molten asphalt.

4. Clamps: A clamp is made by connecting two narrow pieces of hard wood by means of two 2½ inch (5.3 cm.) wood bolts. The wood strips measure 15

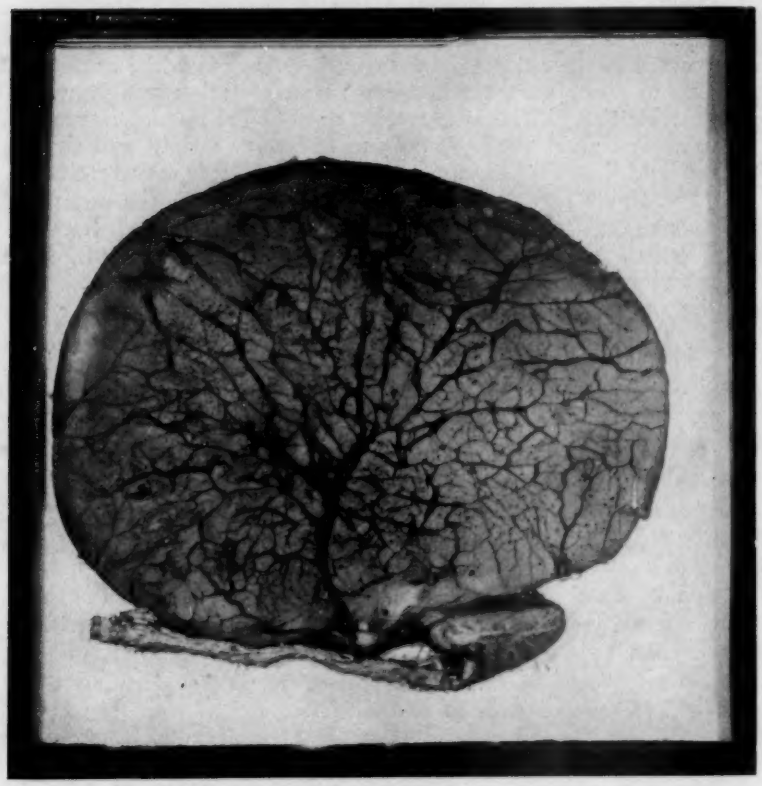

Fig. 1.—A hemisphere of a hydrocephalic brain, in the largest cell in the collection, measuring 15 by 15 by ½ inches. Because of the size, quarter-inch plate glass was used.

by 1¼ by ¾ inch (38 by 3 by 2 cm.) but can be made shorter or longer as desired. The wood bolts are inserted into quarter-inch holes bored at each end. Wing nuts are screwed to the bolts, so that the clamp can be tightened or loosened with ease. Two wood clamps are needed for a small museum cell, but for a very large cell three clamps may be required. Buret clamps should also be available. Occasionally, in the longer specimen jars the tightening of the wood clamps at the ends causes an almost imperceptible bulging in the center of a side. A buret clamp applied at this point results in a close, even approximation from end to end.

5. Clear Duco: A coat of clear duco prevents the brass strip from becoming discolored. The inside of the grooves made by the brass frame and the overlapping edges of the glass should also be painted with clear duco, as this allows the asphalt to adhere more firmly.

Method of Assembling.—The glass plates are cleaned with soap and hot water and wiped dry. The slab of tissue, from which excess moisture has been removed by blotting, is centered on one plate, and the brass frame is placed around it. The second glass plate is placed over the tissue and rests on the brass frame. The loose cell thus formed is placed between two wood clamps, one clamp across the open end and the other clamp at the opposite end. Once the clamps are applied, the glass plates can be properly alined and the tissue and frame accurately centered. The clamp across the open side can be adjusted flush with the edge of the glass, enabling the cell to stand upright. The clamp across the opposite side

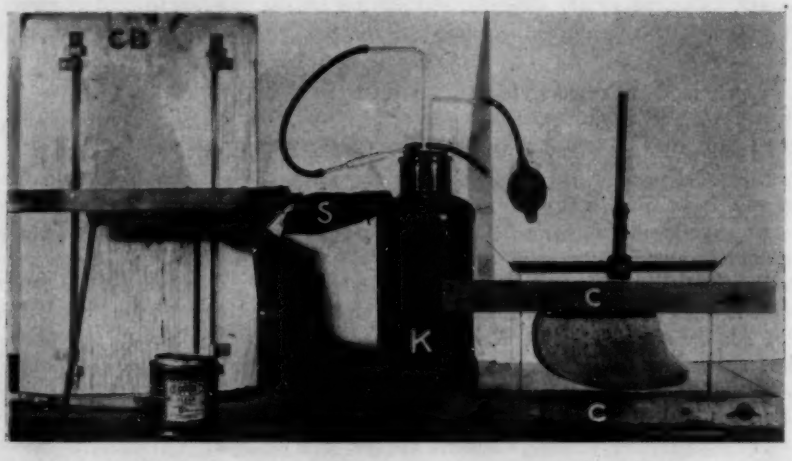

Fig. 2.—Materials used in making a museum cell: *CB* indicates the cutting board; *S*, the spoon in which the asphalt is melted; *K*, the jar with Kaiserling II solution and *C*, the wood clamp.

should be low enough from the edge to permit the brass strip to be seen. This allows enough space for application of the buret clamp.

The inside of the grooves is now coated with clear duco. This is an important step, as the duco creates an excellent adhering surface between the asphalt and the glass. One hour is allowed for the duco to dry.

With the jar standing bottom up, molten asphalt is poured into the groove above the open end. In order to prevent hot tar from running down the sides, metal insertions are temporarily placed in the corners and held in position by a drop of asphalt. Fifteen minutes is allowed for the asphalt in each groove to cool and harden, and then the metal insertions are dislodged.

The same process is repeated for the other two sides, the clamps being readjusted so that they are always parallel to the groove in which the asphalt is being poured. As long as one side is sealed off the loosening and readjustment of the clamps will not cause the glass plates or brass frame to lose their alinement. Metal insertions are also placed in the corners of the open end to prevent the asphalt

from running into the cell. A slow flame can be played along the outside of the black border to smooth out any unevenness or bubbles of air in the asphalt.

When the three sides have been sealed off, fluid is added to test for leaks. If none are present, this practically always being the case, the inner surface of the open end is thoroughly dried. The cell is stood open end up, and the final strip, in which a hole ⅛ inch in diameter has been bored, is inserted. The beveled ends of this piece should fit snugly on the beveled ends of the brass frame uprights. The small hole is covered with a bit of paper, and the upper edge of the frame is filled with asphalt, as described earlier. With a hot needle, the asphalt over the hole is punched through. A 19 gage needle, which is attached to a wash bottle containing Kaiserling II solution [2] is inserted, and by means of the pump action of the rubber bulb on the wash bottle the museum cell is filled with the preserving fluid. One should be sure to turn the cell about, to displace any air bubbles trapped in the tissue. The hole in the asphalt is dried out and closed off with a drop of hot tar. The clamps are removed, and any tar on the faces of the cell is scraped off, and the cell is wiped with some xylene and, finally, washed with soap and water.

PRESERVATION AND CUTTING OF TISSUE

The tissue should be promptly fixed in Kaiserling I solution.[3] Although perfusion has decided advantages, this has not been done with any of our specimens. Specimens of great density, such as liver and spleen, should not be fixed in their entirety, especially if not perfused. Slabs should be cut away and fixed and later cut to more exact thinness. After from twenty-four to forty-eight hours' fixation, depending on the tissue, the specimen is thoroughly washed and is ready for section on the cutting board. As described by Davis and Amolsch, the cutting board is made by securing two parallel ½ or ¼ inch (1.2 or 0.6 cm.) glass rods to a board to act as guides for the knife. The specimen is placed between the glass rods, and a long, thin, flat knife is drawn through it. One need not attempt to make too even or too exact a section, since a little extra thickness holds the tissue more securely when the specimen is placed between the glass plates.

The slab is now placed in alcohol (80 per cent) for several hours, to restore some of the color, and is then preserved in Kaiserling II solution [2] until ready for mounting.

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2. Kaiserling II solution is made up as follows: potassium acetate, 100 Gm.; glycerin, 200 cc.; water saturated with thymol, 1,000 cc.

3. Kaiserling I solution is made up as follows: formaldehyde, 200 cc.; water, 1,000 cc.; potassium nitrate, 15 Gm.; potassium acetate, 30 Gm.

Notes and News

Society News.—The Federation of American Societies for Experimental Biology will meet in Washington, D. C., on March 25, 26, 27 and 28, 1936.

The annual meeting of the American Association of Immunologists will be held in Boston on April 8 and 9, 1936.

The annual meeting of the American Association of Pathologists and Bacteriologists will be held in Boston on April 9 and 10, 1936. One-half day will be devoted to the consideration of inflammation, in a joint meeting with the American Association of Immunologists.

The American Society of Clinical Pathologists will hold its next annual meeting on May 8, 9 and 10, 1936, in Kansas City, Mo. Preceding the meeting a seminar on hematology will be held on May 6, and one on tumors on May 7.

The officers of the Pathological Society of Philadelphia for 1936 are: president, Esmond R. Long; vice president, Baxter L. Crawford; secretary-treasurer, Herbert L. Ratcliffe.

Report on Necropsies in Chicago Hospitals.—The Institute of Medicine of Chicago maintains a committee on necropsies in the hospitals of the city. In its sixteenth report the committee records that 69 of the 76 hospitals in the Chicago area having a capacity of 50 or more beds responded to its questionnaire for 1934. The number of deaths in the reporting hospitals was 17,252; the number of deaths referred to the coroner's office, 2,114, and the number of permission necropsies, 4,649, or 30.7 per cent, as against 29.1 per cent in 1933. Twenty-three hospitals reported that their pathologist spends full time in the laboratory of the hospital; 49 that their pathologist personally makes each necropsy, and 65 that permanent records, available for inspection, are kept of gross and microscopic observations in each case. The committee reports also that progress has been made in the last five years in establishing better cooperation on the part of hospitals, pathologists and undertakers.

Transfer of Laboratories.—According to *The Journal of the American Medical Association,* the Cancer Research Laboratories of the Graduate School of Medicine of the University of Pennsylvania have been transferred to the Franklin Institute and will be continued under the name of Biochemical Research Foundation. Ellice McDonald will continue as director. The president of the university explained in his annual report that the change was made because Irénée du Pont, who established the cancer research department anoymously in 1927, could not agree with the university's policy on the question of rewards for scientific research. Last year the university formally adopted the policy that all discoveries should be made available to the public without any profits accruing to the persons or the institution responsible. Mr. du Pont is said to have expressed the opinion that greater progress would be made if some definite form of financial reward was held forth. He also felt that it would be well for the foundation to patent discoveries with the intent of using profits or income to pay for further research.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Experimental Study of Kupffer Cells. S. Zylberszac, Arch. internat. de méd. expér. **10**:219, 1935.

The cells of Kupffer appear to form a labile syncytium covering blood capillaries. The cells have, in high degree, the power of phagocytosis and adsorption, which stand in inverse relation to the diffusability of the substances acted in. Kupffer cells which have taken up a substance with a high coefficient of diffusion can discharge that substance without degenerating, while cells which have taken up a substance of a low coefficient of diffusion may form masses about the central vein of the lobule and on degenerating liberate their contents. Cells may also become localized in the portal spaces outside the biliary canals. The smallest cells can pass into the central vein and thus reach the lungs. Emboli composed of Kupffer cells may act as foreign bodies and provoke the formation of granulation tissue. Mitosis may take place in Kupffer cells even when they are engaged in phagocytosis. Kupffer cells may be carried by the blood current toward the central vein or by the biliary current into portal spaces about the biliary canals.

From the Author's Summary.

Experimental Production of Tubular Contracted Kidney Caused by Ligation of the Renal Vessels. R. Maatz, Frankfurt. Ztschr. f. Path. **46**:438, 1934.

The left renal arteries and veins of nineteen white rats were ligated temporarily (over a period of from one and one-half to two hours) and the animals allowed to recover; ten were killed from three to four days later and seven at intervals of four weeks each. Two were kept for an indefinite period. Most of the changes were found in the tubules, particularly in the convoluted tubules. There was much necrosis of the lining cells with formation of granular and hyaline casts and casts filled with red blood corpuscles. Also a few small areas of necrosis were found throughout the kidneys. About one month after the temporary ligation was applied, the kidneys became smaller, contracted and granular. The cortex was reduced, and the glomeruli seemed closer to one another but unchanged. Many tubules close to the glomeruli were replaced by connective tissue, so that some glomeruli appeared as islands among the newly formed connective tissue. The arteries, veins and capillaries showed no histologic changes. The belief is expressed that the preservation of the glomeruli and the disappearance of convoluted tubules are in favor of the assumption that in nephrosclerosis of the arterial variety the tubules are damaged first and the glomeruli secondarily. Because the vessels showed no changes, Maatz believes that in some instances of contracted kidney, which today is thought to be of vascular origin, the parenchymatous changes may be primary, while the changes in the blood vessels occur secondarily.

Otto Saphir.

Effect of Administration of Split Products of Bone and Bone Marrow of Chickens on Bone Formation and Hematopoiesis in Chickens. W. Gohs, Frankfurt. Ztschr. f. Path. **46**:453, 1934.

Repeated parenteral administration of bone and marrow treated with x-rays and preserved in 50 per cent glycerin to previously healthy chickens resulted in the production of giant cell sarcoma-like tumors and bone cysts—a picture grossly resembling fibrous osteitis—and disturbances in hematopoiesis (erythremia, anemia

and leukemic conditions). By the administration of the bone and marrow of affected animals to healthy chickens both of these conditions could be transmitted. The bone changes could be produced in healthy chickens merely by exposing the latter to diseased chickens in the same cages. In these instances the changes in the blood were less severe. Enlargement of the parathyroid glands and also in some cases of the adrenal glands was observed in affected animals. Gohs believes that the specific pathogenic agent contained in bone and bone marrow split products produces its action in a manner similar to that of bacteriophage.

FROM THE AUTHOR'S SUMMARY.

FUNCTIONAL ACTIVITY IN THE EXPERIMENTAL PRODUCTION OF HYPERERGIC CORONARY AND PULMONARY ARTERITIS. R. KNEPPER and G. WAALER, Virchows Arch. f. path. Anat. **294**:587, 1935.

It has been previously shown by Klinge and others that it is possible to cause an allergic coronary arteritis histologically similar to that which occurs in acute rheumatic infection, but that large shock or activating doses (20 to 30 cc.) of the antigen are necessary. In Knepper and Waaler's experiments rabbits were sensitized to horse or swine serum by subcutaneous injections. The sensitized animals were vigorously exercised in an electric treadmill, the object being to cause increased functional activity of the heart and lungs. In animals so treated small intravenous injections of from 2 to 3 cc. of the antigen were sufficient to cause a hyperergic proliferative inflammatory reaction of the branches of the coronary and pulmonary arteries.

O. T. SCHULTZ.

Pathologic Anatomy

CHANGES IN THE TERMINAL NERVES OF MUSCLE IN RHEUMATIC INFECTION. H. KAISERLING, Virchows Arch. f. path. Anat. **294**:414, 1935.

This is another in the series of contributions by Klinge and his associates on the pathology of rheumatic infection. The changes occurring in the muscles in acute rheumatic fever have been previously described. Whether, in the absence of such alterations in the voluntary musculature, involvement of the terminal nerves accounts for the muscular pain in rheumatism remained an open question. The material used for the study of this question was muscle tissue from a woman, aged 28 years, who died of mitral endocarditis in a recurrent attack of rheumatic fever. The study revealed severe damage to the terminal nerves and their end-plates. The myelin sheaths were swollen, degenerated, broken and in places unstained. The axis-cylinders presented beadlike swellings and were fragmented. The end-plates were disrupted. Such changes may explain the symptomatology of the muscular system in muscular rheumatism.

O. T. SCHULTZ.

CHANGES IN THE THYROID IN INFECTIOUS DISEASES. A. SELZER, Virchows Arch. f. path. Anat. **294**:427, 1935

Two hundred and fifty-four thyroids were examined macroscopically and microscopically to determine whether and in what proportion of cases changes occur in the gland in infectious diseases and whether there is any relation between thyroid reaction and any particular form of specific infectious disease. The material was subdivided according to the diseases represented as follows: acute generalized infectious diseases, 68; chronic generalized infectious diseases, 22; acute inflammation of various organs, 54; chronic disease of organs, 49; other diseases (not infectious), 47; pregnancy, 14. Selzer recognizes two types of reaction: (1) that to acute disease, characterized by epithelial desquamation and proliferation, decrease in colloid content and hyperemia, sometimes with the escape of erythocytes and leukocytes from the vessels; (2) that to chronic disease, consisting in simple atrophy and fibrosis. Changes were observed in the thyroid in 16.5 per cent of the acute diseases and in 26.7 per cent of the generalized

infectious diseases. No relation was evident between the thyroid reaction and any particular form of acute disease. Changes in the thyroid were noted in 6.3 per cent of the chronic diseases and in 22.7 per cent of the chronic infectious diseases. Selzer postulates a predisposition on the part of the thyroid to acute infectious disease and believes that this predisposition may be a factor in the onset of hyperthyroidism following acute infectious disease. O. T. SCHULTZ.

PRESENCE OF IRON IN THE SPLEEN IN LYMPHOGRANULOMATOSIS. B. BERGQVIST, Acta path. et microbiol. Scandinav. **12**:290, 1935.

Iron pigment was found in the spleen in twenty-nine of thirty-seven cases of lymphogranulomatosis. The pigment occurred in brushlike formations, diffusely and in fibrous foci. The brushes occurred only when the spleen showed macroscopic areas of lymphogranulomatosis with connective tissue formation. The way in which the brushes are formed is not clear. The fact that iron may occur in the spleen in lymphogranulomatosis may be of diagnostic significance under certain circumstances.

HETEROTOPY OF GASTRIC MUCOUS MEMBRANE IN SMALL INTESTINE. N. GELLERSTEDT, Acta path. et microbiol. Scandinav. **12**:397, 1935.

Two cases are described in detail. In one the heterotopic tissue was of considerable size; there was no indication of Meckel's diverticulum, and there was peptic ulceration of the intestinal mucous membrane. The second case represented a transition of misplaced gastric tissue into a diverticulum. The genesis of such misplacements is discussed. The presence of gastric mucosa in Meckel's diverticulum is of clinical significance because peptic ulcers may lead to perforation. On account of this possibility the diverticulum may be a dangerous anomaly.

Pathologic Chemistry and Physics

BENCE-JONES PROTEIN EXCRETION AND ITS EFFECTS UPON THE KIDNEY. W. D. FORBUS and OTHERS, Bull. Johns Hopkins Hosp. **57**:47, 1935.

The excretion of relatively large quantities of Bence-Jones protein by the human kidney is accompanied by precipitation of Bence-Jones protein in the tubules in the form of peculiar casts having a fairly constant structure. These casts, being composed of an abnormal protein substance, completely obstruct the tubules and provoke a foreign body reaction, the microscopic picture thus produced being apparently specifically indicative of Bence-Jones proteinuria. The excretion of this protein may be expected to produce a significant anatomic injury to the kidney, provided the quantity excreted is relatively large and the proteinuria prolonged. Disturbance in the function of the kidney will very likely never be serious, but slight diminution in function will probably occur. A persistent moderate elevation of nonprotein nitrogen in the blood and a mild decrease in urea clearance in the presence of persistent relatively pronounced Bence-Jones proteinuria would, therefore, most likely establish a clinical diagnosis of a specific lesion of the kidney and make possible a fairly accurate prediction of the state of the kidney. FROM THE AUTHORS' SUMMARY.

THE EFFECT OF PARATHYROID EXTRACT UPON THE SERUM CALCIUM OF NEPHRECTOMIZED DOGS. R. ELLSWORTH and P. H. FUTCHER, Bull. Johns Hopkins Hosp. **57**:91, 1935.

In three nephrectomized dogs parathyroid extract produced a marked rise in serum calcium. A slight rise was observed in nephrectomized animals that did not receive parathyroid extract. Following nephrectomy, in both groups of animals the volume of plasma relative to that of the cells tended to increase. Observations of the concentration of protein in the plasma as well as the

hematocrit readings showed no hemoconcentration. The observed rise in calcium may be interpreted as a mobilization of calcium into the blood. The inorganic phosphate of the plasma, as well as the nonprotein nitrogen, as would be expected, rose. A very high calcium-phosphorus product resulted. The significance of this is discussed. It is concluded that the elimination of inorganic phosphorus in increased amounts by the kidneys, commonly observed after the injection of parathyroid extract, is not necessary in the dog for the production by that extract of an elevation of serum calcium, since the elevation occurred in the absence of the kidneys.

FROM THE AUTHORS' SUMMARY.

CHRYSIASIS FOLLOWING TREATMENT BY GOLD SALTS. W. C. FOWLER, Tubercle **16**:539, 1935.

Four cases of chrysiasis following treatment with a double thiosulfate of sodium and gold (sanocrysin) and another possible case in connection with herpes zoster are described. The occurrence of chrysiasis is sometimes overlooked because its appearance is often delayed until a year or more after treatment has ceased. The bluish-purple discoloration of the skin of the face, chin, neck and any part of the chest exposed to light is noted. On pressure of the skin under a glass slide the color is blue. The bed of the finger-nails also appears blue on pressure. Color is noticeable in the upper and lower eyelids except in the folds. Chrysiasis appears to be definitely a photographic effect, fluctuating according to the degree of exposure to light, and associated with a deposition of gold in the deeper layers of the skin, as shown by microscopy and by incineration.

H. J. CORPER.

THE COPPER CONTENT OF THE LIVER AND OTHER ORGANS. W. GERLACH, Virchows Arch. f. path. Anat. **294**:171, 1934.

The quantity of copper in the liver and other organs was determined in a large number of cases by the method of spectroscopic analysis.

The copper content of the liver after the first year of life varied from 2 to 40 γ per gram of fresh tissue. In the fetal period much higher values were observed, up to 250 γ, with an average of 67.9. During the first year of life there was a progressive decrease in the copper content of the liver. At birth there was no correlation between the copper content of the liver and the amount of hematopoietic tissue. The average copper content of the liver in twenty-five cases of various forms of cirrhosis was 38.3 γ. In cases of typical Laënnec's cirrhosis it varied from the normal to 180 γ.

The spleen contained from 0.9 to 10 γ of copper; the upper limit was not exceeded even when the copper content of the liver was very high. The average copper content of the lung was 2.5 γ and that of the kidney 2.98. In other human tissues the quantity of copper varied from 1 to 6 γ per gram of substance.

O. T. SCHULTZ.

QUANTITATIVE DETERMINATION OF HEAVY METALS IN TISSUES BY SPECTROSCOPIC ANALYSIS. K. RUTHARDT, Virchows Arch. f. path. Anat. **294**:198, 1934.

The method of quantitative spectroscopic determination of heavy metals in tissues, which has led to numerous contributions from Gerlach's institute in Basel, Switzerland, has been developed so that it is now possible to estimate successively in a single small sample of material the various heavy metals.

O. T. SCHULTZ.

STRONTIUM AND BARIUM IN HUMAN TISSUES. W. GERLACH and R. MÜLLER, Virchows Arch. f. path. Anat. **294**:211, 1934.

By spectroscopic analysis, strontium has been found to be uniformly present in human tissues. The quantity varies from 0.1 to 1 γ per gram of fresh tissue,

being highest where calcium is highest. Although the method used detects quantities of barium as small as 0.01 to 0.05 γ, barium has not been found in human tissues.

O. T. SCHULTZ.

Microbiology and Parasitology

THE INFECTIVITY OF TREPONEMA PALLIDUM IN EXCISED SYPHILITIC TISSUE. P. D. ROSAHN, Am. J. Hyg. **22**:283, 1935.

Under ether anesthesia, rabbits with active syphilitic orchitis were castrated, and the syphilitic tissue was stored at refrigerator temperature. At intervals varying from twenty-four hours to forty-two days, portions of the refrigerated syphilomas were ground up with saline solution and inoculated into test rabbits intratesticularly. Positive infections as determined by the clinical development of syphilitic lesions or by successful subinoculations of excised lymph nodes were obtained with syphilitic material which had been stored in the refrigerator for twenty-four hours, forty-eight hours, ninety-six hours and seven days. Negative results were obtained with material stored for fourteen, twenty-three and forty-two days. The infections varied with the age of the material from a typical disease to one of more than usual severity and finally to an asymptomatic infection which could be demonstrated with certainty only by subinoculation. It is suggested that in certain instances of human syphilis without a history of a primary lesion the infection may have been initiated by attenuated spirochetes, and that occasionally contaminated material, especially fomites from syphilitic patients, may be the source of attenuated spirochetes. Spirochaeta pallida in autopsy material which has been refrigerated for as long as seven days should be regarded as infectious.

FROM THE AUTHOR'S SUMMARY.

A COMPARISON OF THE ROENTGENOLOGICAL AND PATHOLOGICAL FINDINGS IN EXPERIMENTAL PULMONARY TUBERCULOSIS IN RABBITS. H. E. BURKE, Am. Rev. Tuberc. **32**:343 and 382, 1935.

Primary experimental pulmonary tuberculosis comparable in many ways to pulmonary tuberculosis in children was produced in rabbits by intratracheal injection of measured quantities of virulent human tubercle bacilli. Reinfection tuberculosis comparable in many ways to pulmonary tuberculosis in adults was produced in rabbits by injecting avirulent bacilli (amount not definitely measured) into the groins of the animals and subsequently (approximately three weeks later) injecting measured quantities of virulent human tubercle bacilli into these animals intratracheally. The roentgenologic observations in the rabbits with reinfection tuberculosis differed from those in the rabbits with primary experimental pulmonary tuberculosis in that abnormal shadows appeared sooner, attained greater size earlier, and began to recede sooner. No shadow or combination of shadows in the chest or excised lung served to distinguish the lesions of reinfection from those of primary pulmonary tuberculosis. Large areas of tuberculous pneumonia which undoubtedly contained caseous foci frequently healed by resolution. Attention is called to the striking resemblance between reinfection tuberculosis produced experimentally in the lungs of rabbits and clinical pulmonary tuberculosis in adult human subjects.

H. J. CORPER.

CONGENITAL SYPHILIS: DIAGNOSIS BY DARK-FIELD EXAMINATION OF SCRAPINGS FROM UMBILICAL VEIN. N. R. INGRAHAM JR., J. A. M. A. **105**:560, 1935.

Dark-field examination of the umbilical vein disclosed syphilis in nineteen of eighty-seven living offspring of syphilitic mothers at a time in the infant's life when most other clinical criteria and laboratory aids are unsuccessful. Since thirty-five of the living infants were proved by observation to have syphilis, a negative dark-field examination does not rule out syphilis but indicates the necessity of studying the infant by other methods. The fact that in 54 per cent

of the syphilitic children the disease was diagnosed within a few hours after birth indicates that this method has a diagnostic value which somewhat overshadows its cumbersomeness. It is unpractical to examine a specimen of the cord at every delivery in a large maternity service, but when the diagnosis of syphilis is made in the mother, as it should be, before delivery takes place, such specimens can be examined without placing too great a burden on the physicians in charge, and the diagnosis of congenital syphilis can be established immediately in a limited number of cases.

ELEMENTARY BODIES OF VACCINIA. R. F. PARKER and T. M. RIVERS, J. Exper. Med. **62**:65, 1935.

By differential centrifugation in the horizontal and angle centrifuges it is possible to obtain appreciable quantities of relatively pure elementary bodies of vaccinia. Such preparations of elementary bodies exhibit an extremely high titer of vaccine virus. The elementary bodies are specifically agglutinated by serum from rabbits immunized by injections of bacteria-free vaccine virus. Virus-free filtrates of dermal vaccine virus and of bacteria-free testicular vaccine virus contain a soluble substance or substances that are precipitated by antivaccinal serum.

FROM THE AUTHORS' SUMMARY.

INTERSTITIAL BRONCHOPNEUMONIA. D. H. SPRUNT, D. S. MARTIN and J. E. WILLIAMS, J. Exper. Med. **62**:73, 1935.

Bacterial toxins can produce pneumonia similar to that caused by viruses, and the presence of a toxin-producing bacterium in the lungs may account for the interstitial bronchopneumonia observed in some cases of diseases other than those caused by viruses.

FROM THE AUTHORS' CONCLUSIONS.

THE EPIDEMIOLOGY OF PSEUDORABIES. R. E. SHOPE, J. Exper. Med. **62**:85 and 101, 1935.

Pseudorabies is an often fatal but noncontagious disease of cattle and the common laboratory animals. It is a relatively mild yet highly contagious disease of swine. In swine it has been shown that the nose serves for both the entrance and the exit of the virus. Furthermore, it has been observed that fatal pseudorabies can be induced in rabbits merely by bringing abraded areas of their skin into contact with the noses of infected swine. The blood serum of swine on two farms where pseudorabies had occurred in the cattle was found to be capable of neutralizing pseudorabies virus. It is believed that the swine had a mild and unrecognized pseudorabies and transmitted their disease to the cattle by transfer of the virus on their noses to abraded areas in the skin of the cattle.

Study of the neutralizing antibody content of pooled and individual samples of swine serum have led to the conclusion that pseudorabies is highly prevalent but unrecognized in middle-western hogs. It has been shown that a fatal infection develops in wild brown rats following ingestion of pseudorabies virus and that their carcasses on being fed to swine give rise to the disease. It is believed that rats serve as the initial source of the infection for swine herds and also as one means by which the virus can be spread from farm to farm. The experiments presented furnish further evidence that swine may serve as the source of pseudorabies in cattle.

FROM THE AUTHOR'S SUMMARY.

THE TRANSMISSION OF EQUINE ENCEPHALOMYELITIS VIRUS BY AEDES AEGYPTI. M. H. MERRILL and C. TEN BROECK, J. Exper. Med. **62**:687, 1935.

In confirming Kelser's work on the transmission of equine encephalomyelitis of the western types by Aedes aegypti it has been learned that the mosquitoes must be fed virus of high titer if positive results are to be secured. A period of from four to five days after feeding either on infected guinea-pigs or on brain containing

virus must elapse before the disease is transmitted by biting, but after this time transmission regularly results for a period of about two months. By inoculation virus can be demonstrated in the bodies of infected mosquitoes for the duration of life. Although virus multiplies in the mosquitoes and is generally distributed in their bodies, repeated attempts to demonstrate it in the eggs from females known to be infected as well as in larvae, pupae and adults from such eggs have been uniformly without result. Larvae have not taken up virus added to the water in which they live. Male mosquitoes have been infected with virus by feeding, but they have not transmitted the virus to normal females, nor have males transmitted the virus from infected to normal females. When virus of the eastern instead of the western type is used, transmission experiments with Aedes aegypti result negatively. Apparently this virus is incapable of penetrating the intestinal mucosa of the mosquito. If, however, it is inoculated into the cavity of the body by puncture with a needle it persists, and transmission experiments result positively.

FROM THE AUTHORS' SUMMARY.

BENIGN LYMPHOCYTIC CHORIOMENINGITIS (ACUTE ASEPTIC MENINGITIS). C. ARMSTRONG and P. F. DICKENS, Pub. Health Rep. **50**:831, 1935.

A symptom complex of headache, fever, meningeal irritation, increased pressure of cerebrospinal fluid, increase in cells of the fluid above 50 (with a lymphocytic response dominant), coupled with a normal content of chloride, sugar and urea in the fluid and a negative Wassermann reaction of the fluid, is a clinical entity which in man has previously been designated as acute aseptic meningitis. The virus of Armstrong produces a similar symptom complex in monkeys. The blood serum of patients who have recovered from the disease protects animals from the virus reported by Armstrong (National Institute of Health strain). The disease occurs sporadically in man and has been transferred experimentally to animals. Traub has isolated a virus from white mice and Rivers and Scott a virus from patients both of which are serologically identical with the National Institute of Health strains of the Armstrong virus. Cases reported in this paper and by Dickens and Armstrong had their origin in California, Maryland, the District of Columbia, Illinois, Ohio and Virginia. This condition by reason of priority should be designated "acute aseptic meningitis," but in view of the recent advance in the knowledge of its causation the designation is a misnomer. The authors suggest the designation "acute lymphocytic choriomeningitis" as more accurate.

FROM THE AUTHORS' SUMMARY.

CULTIVATION OF THE VIRUS OF ROCKY MOUNTAIN SPOTTED FEVER IN THE DEVELOPING CHICK EMBRYO. I. A. BENGTSON and R. E. DYER, Pub. Health Rep. **50**:1489, 1935.

The virus of Rocky Mountain spotted fever was cultivated in developing chick embryos and maintained through twenty passages without diminution in virulence for either the embryos or guinea-pigs. There was, on the other hand, some evidence of increase in virulence for the embryos, as they died earlier in the late generations. Guinea-pigs inoculated with the virus that had passed through embryos had fever earlier and died on the average one day earlier than those inoculated with the virus that had been maintained in guinea-pigs. The virus was apparently more virulent for the embryos than for the guinea-pigs, as the embryos usually succumbed on the fifth or sixth day after inoculation, while the average period of survival of the guinea-pigs was seven days. The chorio-allantoic membrane was at times infective for guinea-pigs in dilutions up to 1:10,000. The virus was present in the brain and liver of the embryo, but the concentration of virus was lower in the brain than in the membrane. Typical rickettsiae were present in the epithelial cells of the membrane. The fact that rickettsiae were present in passage material far removed from the original material used for initiating growth lends support to the view that these organisms are concerned as the causative agent of the disease.

FROM THE AUTHORS' SUMMARY.

Immunology

A Standardized Tuberculin (Purified Protein Derivative) for Uniformity in Diagnosis and Epidemiology. E. R. Long, F. B. Seibert and J. D. Aronson, Tubercle **16**:304, 1935.

Old tuberculin cannot be made uniformly because of inherent inconstancies in its manufacture, and it is therefore not a suitable standard. The active principle of old tuberculin can be isolated and put up in dry form. The refined form is designated "purified protein derivative." Optimum dosages of this substance for epidemiological work and for testing of tuberculous children and adults are given. Several series of tests in the United States, England and Wales are reported here, in some of which a comparison with old tuberculin and roentgen observations has been recorded. The roentgen examinations indicate that the purified protein derivative, like other tuberculins, may fail to detect an occasional case of healed primary tuberculosis with calcified foci, but cases of clinical significance are not missed.

H. J. Corper.

Diphtheria Antitoxin in Human Colostrum and in Mother's Milk. Jeanne van den Hoven van Genderen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:54, 1934.

In the colostrum of thirty-three of forty-three women examined diphtheria antitoxin was found in quantities varying between 1/500 and 1/50 antitoxin unit per cubic centimeter. The amount was always smaller than that in the blood serum of the mother, but the two levels were distinctly related to each other. Ten days post partum the antitoxin in the milk of the mothers was either very low or entirely absent so that, according to the author, the antitoxin in the milk of the mothers could not have been the source of the antitoxin which was found in the blood of the infants.

I. Davidsohn.

The Influence of Acid or Alkali on the Anaphylactic Shock. E. Rentz and A. Kaktin, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:59, 1934.

Guinea-pigs were sensitized with beef serum and fed hydrochloric acid or sodium carbonate for three weeks. The acidotic animals reacted to the reinjections more severely than the alkalinized ones. The result seems to contradict clinical experience, but on closer analysis it is found to agree fully with the known facts of the relation between acute and chronic acidosis and alkalosis and the calcium metabolism.

I. Davidsohn.

The Influence of Temperature and Time on the Fixation of Complement by the Subgroups A_1 and A_2. F. Hahn, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:95, 1934.

That the differences between subgroups A_1 and A_2 are quantitative can be demonstrated by complement-fixation tests in which an antiserum produced by injecting blood cells of either subgroup A_1 or A_2 into rabbits is tested with alcoholic extracts of the red cells of the two subgroups. The antiserum reacts with both extracts if proper quantities are used, and on the other hand no fixation takes place with the extract of A_2 if the quantity employed is below the necessary minimum. Lowering of the temperature and shortening of the time of incubation permitted a differentiation between the two extracts even when the quantitative factor was eliminated by the use of sufficiently large doses. The extracts of A_2 did not react or reacted markedly less at low temperatures and required considerably more time to become apparent; this indicates a lower avidity of the A_2 substance. The extract of subgroup A_2B reacted only very slightly at any temperature, and differences were noted between different samples of A_1B which could not be

detected with other methods. No differences were noted in the properties of the serums of rabbits immunized with A_1 or A_2 cells, while those from guinea-pigs thus immunized reacted only with extracts of A_1 red cells. I. DAVIDSOHN.

ATTEMPTS TO ISOLATE WATER-SOLUBLE GROUP-SPECIFIC SUBSTANCES FROM HUMAN ERYTHROCYTES. C. HALLAUER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:114, 1934.

The preliminary extraction of red blood cells with alcohol permitted one subsequently to obtain a greater yield of water-soluble group-specific substances. Their group specificity and high concentration were demonstrated by their reaction with iso-agglutinins and, for the A substance, by absorption of A-specific antisheep hemolysins produced by immunizing rabbits with A erythrocytes. The existence of a group-specific O substance was confirmed. It can be demonstrated by the use of certain ox serums which possess a specific anti-O hetero-agglutinin. The water-soluble group-specific substances failed to produce specific antibodies in rabbits, even when hog serum was added. The substances O, A and B were soluble in water but insoluble in alcohol, ether, acetone and cold benzene. Chemical analysis demonstrated the absence of protein and the presence of carbohydrates, phosphorus, nitrogen and sulphur. I. DAVIDSOHN.

THE TOXIN OF BACILLUS PERTUSSIS. E. F. TRUSCHINA and others, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:124, 1934.

Concentrated filtrates of cultures of four strains of the Bordet-Gengou bacillus were found to be highly resistant to heat. They produced specific immune serums when injected into rabbits. Mice immunized with the toxin became resistant to fatal doses. Treatment with solution of formaldehyde changed the toxin into an anatoxin. Skin tests showed more positive reactions in persons who had never had pertussis than in those who had. I. DAVIDSOHN.

THE COMPLEMENT FRACTIONS IN COMPLEMENT FIXATION. T. MISAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:130, 1934.

The fourth fraction (a thermostable portion which is destroyed by ammonia) is the one mainly affected in complement fixation. The thermolabile, so-called middle fraction (*Mittelstück*) is also more or less destroyed in direct proportion to the degree of complement fixation. The same changes occur in the course of nonspecific complement fixation. Preliminary observations are reported according to which addition of inactivated guinea-pig complement to fresh active complement interfered with the fixation of complement but only in the presence of small amounts of antiserum. I. DAVIDSOHN.

TOXIN OF THE TYPHOID BACILLUS. E. B. GINSBURG and others, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:143, 1934.

A highly thermostable toxin was demonstrated in young broth cultures of the typhoid bacillus. It was highly toxic for mice, less so for rabbits. It reacted with antityphoid immune serums in precipitation, complement-fixation, and neutralization tests. It stimulated the production of specific antiserums in rabbits. I. DAVIDSOHN.

THE ANTIGENS IN MILK. W. JADASSOHN and F. SCHAAF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:152, 1934.

The technic of Schultz and Dale proved suitable for the study of the milk of cows, of goats and of rabbits. A common antigenic substance was found in the milk of these three species, but in the rabbit the antigenic property was of a hapten-like character; i. e., when rabbit milk was added to the bath containing

the uterus of a guinea-pig that was sensitized to either cow's or goat's milk a contraction of the uterus took place, but when cow's or goat's milk was added to a bath containing the uterus of a guinea-pig sensitized to rabbit's milk a contraction of the uterus did not take place, showing that when a guinea-pig is sensitized with rabbit's milk a sensitization to cow's or goat's milk does not occur simultaneously. Antigenic substances were discovered which were common to the milk and the serum, but they were also present in the serums of other species. The milk of cows and of goats contains also an antigenic substance specific for it and not present in the homologous blood or in the heterologous milk.

I. DAVIDSOHN.

THE THERMOSTABLE FRACTIONS OF THE COMPLEMENT IN THE SERUMS OF DIFFERENT SPECIES. T. MISAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:177, 1934.

The complementary action of the serums of different species was compared with the action of the same serums when heat-inactivated and mixed with the thermostable third and fourth fractions of guinea-pig's serum. Marked variations in the contents of these thermostable fractions in the serums of the different species were found. Guinea-pig's serum is rich in both the third and fourth fractions; human serum abounds in the fourth fraction but not in the third. The third fraction is more abundant in the serums of rabbits, rats, hogs, dogs, oxen and sheep.

I. DAVIDSOHN.

CONTRACTIONS OF SMOOTH MUSCLES DUE TO SNAKE VENOM; THE ACTION OF FORMALDEHYDE. H. BERNKOPF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:197, 1934.

The contractions of the isolated uterus of the guinea-pig caused by the venom of the tiger-snake resemble much more closely anaphylactic contractions than the contractions caused by histamine. The venom of other snakes differed from that of the tiger-snake in many ways, among others by the production of tetanic contractions. Addition of formaldehyde to the bath in which the organ was suspended inhibited the contraction. Replacement of the Ringer solution by fresh Ringer solution without the formaldehyde caused a contraction of the uterus. This suggests that the formaldehyde acts directly on the muscle.

I. DAVIDSOHN.

HETERO-ALLERGY IN TUBERCULOSIS. J. WEISSFEILER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:203, 1934.

The interpretation of the phenomenon of Koch (exudation, demarcation and necrosis following intracutaneous injection of tubercle bacilli into tuberculous animals) as evidence of immunity has been abandoned. Important arguments have been gathered even against its specificity. Weissfeiler took up the problem and found that in guinea-pigs infected with the human type of tubercle bacilli and in rabbits infected with the bovine type there were individual differences in the cutaneous reaction to reinfections but that these differences did not depend on the type or the virulence of the injected bacteria. Furthermore, not only the tubercle bacilli but a great variety of heterologous bacteria (acid-fast saprophytes, actinomycetes, diphtheroid bacilli, etc.) were also able to produce the typical Koch phenomenon. In animals infected with an acid-fast saprophyte (Friedmann's bacillus) and then reinfected with the same bacillus the typical Koch phenomenon was produced, but when true tubercle bacilli were used for the reinjection a cutaneous lesion developed which did not differ from the Koch phenomenon but which did not heal and led to a true tuberculous infection. This indicates that the Koch phenomenon does not depend on the existence of immunity. The phenomenon is not a specific reaction of the tuberculous animal, but a change in the reactivity of the tuberculous animal against bacteria in general.

I. DAVIDSOHN.

AVITAMINOSIS AND RESISTANCE AGAINST INFECTIOUS DISEASES. ANNEMARIE HEINICKE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:245, 1934.

For four weeks white rats were fed a diet free from vitamin D and poor in phosphorus (McCollum diet no. 3143). Rickets developed, and the blood serum showed a decrease of bactericidal properties against typhoid bacilli as compared with normal controls. There was no difference in the complementary properties of the serum.

I. DAVIDSOHN.

SERUMS FROM GUINEA-PIGS IMMUNIZED AGAINST HUMAN BLOOD A_1 AND A_2. F. HAHN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:257, 1934.

Guinea-pigs were immunized with A_1 and A_2 red cells. More frequently than rabbits they produced group-specific immune serums, but these serums were of considerably lower titers. In anti-A_2 serums species-specific antibodies were often more abundant, while in anti-A_1 serums the group-specific antibodies prevailed. This was particularly noted in immune serums produced with A_1B and A_2B red cells. Serums produced with A_1 and A_2 cells frequently agglutinated the A_1 cells in higher titers than the A_2 cells. Subgroup-specific agglutinins, i. e., those acting exclusively on A_1 or A_2 cells, were not demonstrated. However, anti-A_1 and anti-A_2 immune serums fixed complement with alcoholic and aqueous extracts only of A_1 cells.

I. DAVIDSOHN.

THE AGGRESSINS OF GONOCOCCI AND OF MENINGOCOCCI. H. BURKHARDT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:297, 1934.

Extracts of bacterial bodies were prepared by various methods: heating of bacterial suspensions, extracting with distilled water, freezing and thawing, etc. Such extracts of gonococci did not act like aggressins; i. e., when added to the bacteria they did not permit one to decrease the fatal dose. With one or two strains of meningococci aggressins were produced which lowered the fatal dose for mice to 1/150 of the original.

I. DAVIDSOHN.

THE GROUP-SPECIFIC DIFFERENTIATION OF FECES. I. MOHARREM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:312, 1934.

Aqueous extracts of feces of groups A and B contain the group-specific iso-agglutinogens, as evidenced by inhibition of the iso-agglutinating properties of proper human serums. Alcoholic extracts lacked this ability, but those of group A inhibited the hemolytic properties of an antisheep lysin produced by injections of A blood, while alcoholic extracts of groups B and O had no such effect. Aqueous extracts of feces of group O inhibited hetero-agglutination by an anti-O immune serum. Contrary to the findings in the saliva, no differentiation of persons into eliminators and noneliminators of the group-specific substances was demonstrable. The ferment which destroys the blood group substances in the feces affects the water-soluble but not the alcohol-soluble fraction.

I. DAVIDSOHN.

THE ANTIPNEUMOCOCCUS BACTERIOLYSINS. A. PETTERSSON, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:335, 1934.

In addition to the complement there is present in the body fluids another bacteriolytic substance called by Patterson β-lysin. Both of these lytic substances act on carious bacterial species. The bacteria which are susceptible to β-lysin are unable to stimulate in animals the production of bacteriolytic antibodies. Pettersson confirmed the well known fact that most animal serums possess only very faint bactericidal properties against pneumococcus. The serums of man and the hog have somewhat higher pneumococcidal properties, which have the characteristic features of the β-lysins. They are relatively thermostable and cannot be removed by extraction with ether or by dialysis. The inability of Pneumococcus

to produce bacteriolytic immune serums is in line with the lack of similar antigenic properties in other bacteria sensitive to the β-lysin. Leukocytic extracts had bactericidal properties against Pneumococcus, but monocytic extracts were inert.

I. DAVIDSOHN.

THE INFLUENCE OF THYROID PREPARATIONS ON ANAPHYLAXIS IN GUINEA-PIGS. T. BLOM, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:373, 1934.

A marked increase of anaphylactic phenomena was observed following administration of different commercial thyroid preparations and of compound solution of iodine.

I. DAVIDSOHN.

THE INFLUENCE OF LIVER EXTRACT ON ANAPHYLAXIS IN GUINEA-PIGS. H. WOLF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:381, 1934.

Guinea-pigs were sensitized with pea protein. Administration of two different liver extracts brought about slight to moderate reductions of the anaphylactic phenomena, but only when a proper dosage was given; otherwise, the effect was the opposite.

I. DAVIDSOHN.

THE ACTION OF ANTIPNEUMOCOCCUS SERUM. L. OELRICHS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:390, 1934.

That the action of antipneumococcus serum is species-specific and type-specific was shown on rabbits which were inoculated with pneumococci of types I and II and staphylococci and treated with various immune serums. The action of the antiserums was estimated by the number of colonies which grew from blood samples taken at various intervals. When pneumococci were mixed with a specific antiserum and then washed and injected into animals the effect was similar to that when the immune serum was injected directly into the animal. The bacteria, pneumococci as well as streptococci, are taken up by the spleen, which swells up considerably. Pneumococci are clumped, and the capsules swell.

I. DAVIDSOHN.

CHANGES IN THE SERUM PROTEINS FOLLOWING INJECTIONS OF ANTIGENIC AND NONANTIGENIC SUBSTANCES. T. WOHLFEIL and A. HEYMER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:409, 1934.

Quantitative determinations of tryptophan and tyrosine in the serums of normal and immunized guinea-pigs were carried out. A marked increase of tryptophan was found following repeated injections of foreign serum, of red cells and of typhoid bacilli. The injection of the soluble antigen-like serum led mainly to a rise of the globulin, while after the introduction of the cellular antigens the total protein was also elevated. A nonantigenic substance like gelatin caused a rise of tryptophan but only under proper experimental conditions (when dissolved in a tenth-normal solution of sodium hydroxide). However, this increase was due to local destruction of tissue at the site of the injection. Single injections of large amounts of serum caused marked rises of tryptophan due to an increase of globulin. Similar large amounts of gelatin brought about moderate increases of tryptophan which were due to a rise of the total serum protein. The frequency of inoculations and the interval between the last inoculation and the examination of the serum influence greatly the level of the tryptophan.

I. DAVIDSOHN.

Tumors

THE EFFECT OF PROTEIN ON THE SWELLING OF NORMAL AND TUMOR CELLS. M. J. SHEAR, Am. J. Cancer **23**:771, 1935.

The swelling exhibited by normal tissue cells and by tumor cells of mice in salt solutions is retarded by increasing the protein content of the solution. With

high concentrations of protein the swelling is almost entirely inhibited. The swelling which occurs in salt solutions is reversed on transfer of the cells to protein solutions. The flow of water into and out of solid tissue cells of mice appears to be governed by the protein content of the external medium and not by the salt content.

FROM THE AUTHOR'S SUMMARY.

CHONDROSARCOMA. B. HALPERT and J. B. DAVIS, Am. J. Cancer **23**:784, 1935.

Records of two patients with chondrosarcoma are presented. In one the growth was primary in the tibia and at the time of amputation of the limb involved the patella, femur and skin. In the other the growth was primary in the rib, involved the spinal epidural space, causing compression and necrosis of the spinal cord with complete paralysis of the parts distal to the area of involvement, and metastasized into the lungs. In each instance the growth was a pure chondrosarcoma with the structure of embryonal cartilage, occurred in a patient past the age of skeletal development, and was not diagnosed finally until the growth reached an advanced stage.

FROM THE AUTHOR'S SUMMARY.

METASTASIS OF CARCINOMA FROM THE WRIST TO THE AXILLA WITHOUT DEMONSTRABLE INTERVENING GROWTH. E. R. LONG, Am. J. Cancer **23**:797, 1935.

In a case of squamous cell carcinoma of the wrist with metastases in the axillary lymph nodes, cross-sections were studied from blocks cut serially through the wrist, forearm, elbow and lower third of the upper arm. No carcinoma was seen in the lymphatics or in any other structure of the arm above a point 1 cm. proximal to the proximal end of the tumor. Granulation tissue reaction to the tumor was evident for an additional distance of 2 cm. In the absence of further evidence of present or past carcinoma between the primary growth and the axillary lymph nodes it could only be concluded that in this case, whether this is the general rule or not, the growth in these nodes resulted from metastasis by lymphatic embolism rather than from continuous extension in the lymph channels.

FROM THE AUTHOR'S SUMMARY.

HISTOGENESIS OF LYMPHOSARCOMATOSIS .J. C. EHRLICH and I. E. GERBER, Am. J. Cancer **24**:1, 1935.

Material from eighteen cases of lymphosarcomatosis revealed varied histologic pictures which could be grouped into three main types on the basis of the morphologic characteristics of the predominating cell type in each case. There were found, first, cases in which large pale cells in reticular arrangement predominated. Then there occurred a group composed of mixed cells, partly reticular, as in the former group, and partly free. The morphology of these free cells resembled that of immature large lymphocytes. Finally, there were encountered cases in which the lymphosarcomatous tissues were composed predominantly of free cells of immature or mature lymphocytic type. These three types were termed, for descriptive purposes, reticular, intermediate and lymphocytic, respectively. These types were found to correspond in their essential morphologic features to the immature, intermediate and mature cells resulting from normal differentiation of the cytoplasmic reticulum along lymphopoietic lines. This similarity, together with evidences of the progressive transformation of the less mature into more mature cell types in lymphosarcomatosis, indicated that the histogenesis of this disease consists of progressive lymphopoietic differentiation of the cytoplasmic reticulum. This process is confined chiefly to the cytoplasmic reticulum of lymphatic tissues, viz., lymph nodes, gastro-intestinal tract, etc. Lymphopoiesis as it occurs in lymphosarcomatosis manifests blastomatous characteristics. These are indicated by the unrestricted growth of the tumor masses and the atypism of the cells. Lymphosarcomatosis arises in a region of lymph nodes, from which it extends to other regions of lymphatic tissue and other organs in progressive fashion.

This spread occurs by direct local extension and by metastasis via the lymphatics and the blood stream. In addition, there occurs autochthonous formation of lymphosarcomatous foci in many centers of lymphatic tissue. This autochthonous origin is evident in partially involved nodes, where intermediate stages in the formation of these foci from local reticulum cells may be observed, and in the diffuse involvement of the malpighian follicles of the spleen in two of our cases. As a result of these modes of spread, lymphosarcomatosis shows in the late stages, in many cases, a widespread involvement of the lymphatic tissues (with the exception of the spleen) and of other tissue. The origin of lymphosarcomatosis simultaneously in various lymph nodes in one region, the autochthonous mode of spread and the tendency toward restriction to one type of tissue separate this disease from true sarcoma. Lymphosarcomatosis bears certain resemblances to lymphadenosis, such as identical histogenesis, restriction to lymphatic tissue and systematization. Nevertheless, the focal origin of the former, the more aggressive character of its growth, the focal involvement of lymph nodes and the limited systematization serve to characterize lymphosarcomatosis as a blastomatous disease of lymphatic tissue, in contrast to the hyperplastic character of lymphadenosis. From an oncologic point of view, lymphosarcomatosis may be classified as a blastomatous disease in the group of hemoblastoses.

FROM THE AUTHORS' SUMMARY.

CELLS OF MELANOMA IN TISSUE CULTURE. C. G. GRAND, R. CHAMBERS and G. CAMERON, Am. J. Cancer **24**:36, 1935.

Mouse and human melanomas have been grown successfully in tissue culture. The implanted fragments tend to render the culture medium very alkaline, and when this occurs no growth takes place. The alkalinity can be neutralized by growing normal tissues in the same medium, whereupon successful growth of the melanoma takes place. Melanoma fragments containing a large proportion of fibrocytes do not give rise to undue alkalinity, and successful growth is obtained without the addition of normal tissues. No epithelial outgrowth has been found in the human melanoma culture nor in the hundreds of cultures grown of the Harding and Passey mouse melanoma. Three types of cells occur in the outgrowth, viz., macrophages, fibrocytes and melanoblasts. The macrophages can be differentiated into actively moving, sparsely laden cells and swollen, sluggish cells densely filled with melanin granules. The fibrocytes with oval nuclei are frequently spindle-shaped. The melanoblasts have spherical nuclei and are highly dendritic. They are morphologically of two kinds: small cells with slender uniform dendrites and large cells with stouter dendrites possessing knobbed swellings along their lengths. The melanin granules in the cells are distributed as follows: In the macrophages they are usually packed in irregular clumps throughout the entire cytoplasm. In the fibrocytes they are massed about the nucleus and are sparse or absent in the pseudopodial extensions. In the melanoblasts they occur in the dendritic processes and only in the periphery of the main cell body. The granules are fine and sparse in the dendrites of the small melanoblasts, while in the large melanoblasts they are more numerous and are collected into clumps, especially in the knobbed swellings. The melanoblasts in the tissue cultures were identified not only by their morphologic appearance but also by their positive reaction to the dioxyphenylalanine reaction.

TUMORS OF THE NEUROMYO-ARTERIAL GLOMUS. A P. STOUT, Am. J. Cancer **24**:255, 1935.

Eleven cases of tumor of the neuromyo-arterial glomus are described, and other reported cases are reviewed, emphasizing anew their small size, slow growth, benign character, subepidermal situation, distribution on the extremities, especially beneath the finger-nails, their association with paroxysms of severe pain and occasionally with manifestations of disturbance of the sympathetic nervous system and their characteristic morphology. A historical review shows that before they

were accurately described and named by P. Masson they were reported under a number of names, such as "angiosarcoma," "perithelioma" and "painful subcutaneous tubercle." Simple incision has resulted in immediate cure of the symptoms in every case, but it is possible for the tumor to reappear long after operation.

FROM THE AUTHOR'S SUMMARY.

THE PHOSPHATASE ACTIVITY OF TISSUES AND PLASMA IN TUMORS OF BONE. C. C. FRANSEEN and R. MCLEAN, Am. J. Cancer **24**:299, 1935.

The phosphatase activity of blood plasma is elevated in osteoblastic sarcoma. It falls and rises with the removal and return of the tumor. A temporary fall occurred in a patient treated with roentgen rays. The authors suggest that the determination of plasma phosphatase may be of value in the diagnosis of metastatic carcinoma of bones and of multiple myeloma.

PROLAN A IN TERATOMA TESTIS. M. CUTLER and S. E. OWEN, Am. J. Cancer **24**:318, 1935.

In patients with teratoma of the testis the amount of prolan A in the urine varied between 50 to 16,000 mouse units, while in the controls the amount was below 50 units per liter. It is recommended that quantitative determinations be made of the prolan A in the twenty-four hour output of urine.

PRIMARY MELANOTIC SARCOMA OF THE ESOPHAGUS. T. C. JALESKI and P. V. WALDO, Am. J. Cancer **24**:340, 1935.

A case of melanotic sarcoma of the esophagus is described in a man of 69. The postmortem examination showed a primary pigmented tumor of the esophagus with metastases to the lungs, liver, pancreas and spine. The presence of melanin in the tumor cells was proved by the use of silver, iron and fat stains, as well as by treatment of the tumor tissue with hydrogen dioxide, acids and alkalis.

FROM THE AUTHORS' SUMMARY.

GIANT-CELL TUMOR OF THE SACRUM INVADING THE VENA CAVA. A. C. FREEMAN, K. K. KINNEY and M. R. MOORE, Am. J. Cancer **24**:345, 1935.

A case of giant cell tumor of the sacrum in a girl 18 years old is described. The growth invaded the retroperitoneal tissues in the pelvis and the inferior vena cava. Trauma may have played a part in its origin.

ON A PECULIAR VASCULAR TRANSPORTATION AND GENERALISATION OF CARCINOMA WITHOUT LOCAL METASTASIS. H. OERTEL, J. Path. & Bact. **40**:323, 1935.

An instance of an abundant intravascular generalization of tumor with growth throughout the viscera but without metastases following on a primary pyloric cancer is recorded. The distinction between metastasis and tumor transportation is emphasized, and the features and bearings of this mode of dissemination are discussed. It is pointed out that so-called "aggressive" and "malignant" properties of tumor cells may be simulated and possibly explained by purely nutritive modifications which their presence imposes on a stationary differentiated tissue. Evidence of a specific antitumor-cell activity of the body was not found in these observations.

FROM THE AUTHOR'S SUMMARY.

ON THE ORIGIN OF TAR TUMOURS IN MICE, WHETHER FROM SINGLE CELLS OR MANY CELLS. J. C. MOTTRAM, J. Path. & Bact. **40**:407, 1935.

The latent period between the application of tar and the appearance of a tar wart can be explained if it is assumed that the wart has origin from a single cell, for it takes several months for a single cell to grow into a visible wart. Calculations show that the latter period of time is comparable with the latent period.

Observations show that the fast-growing tumors, both malignant and benign, tend to appear early, and the slow-growing tumors late, in relation to the time of tarring. This is compatible with origin from a single cell and largely rules out the possibility of origin from many cells. Warts, both malignant and benign, have very constant rates of growth. Change in these rates is rare. In the vast majority of malignant warts no change in rate is found suggestive of a malignant change occurring during their visible life; on the contrary, they appear to be benign or malignant from their first appearance, though then it is often not possible to distinguish between them clinically or histologically but only by autografting.

FROM THE AUTHOR'S CONCLUSIONS.

EXPERIMENTAL INHIBITION OF TUMOUR INDUCTION BY MUSTARD GAS AND OTHER COMPOUNDS. I. BERENBLUM, J. Path. & Bact. **40**:549, 1935.

Several compounds closely related to mustard gas were tested in conjunction with a carcinogenic tar in order to determine whether they possessed the power of inhibiting the induction of tumor. Some of these compounds produced pronounced inhibition while others had no such effect. Among a group of other irritants not related to mustard gas, cantharidin alone was found to possess this property of inhibition to any marked degree.

FROM THE AUTHOR'S SUMMARY.

ADENOLYMPHOMA OF THE SALIVARY GLANDS. R. CARMICHAEL, T. B. DAVIE and M. J. STEWART, J. Path. & Bact. **40**:601, 1935.

Eight new cases of the supposedly rare tumor adenolymphoma of the salivary glands are reported and reports of twenty-six others collected from the literature. Seven of the new cases have been encountered within the past three years, and although they come from various centers in the north of England it would appear that the tumor is by no means a rarity. Adenolymphoma of the salivary glands is a slowly growing benign tumor occurring usually in males. As a rule it first becomes apparent during the fifth or sixth decade of life, usually in the preauricular region or near the angle of the lower jaw. The rate of growth, though slow, is variable, so that the size of the tumor at the time of operation (ranging from that of a cherry to that of a small orange) bears little relationship to the known preoperative duration, which may vary from a few months to twenty or thirty years. Subjective symptoms are absent or slight. The tumor, sometimes soft, sometimes firm and often fluctuant, is well encapsulated and easily enucleated, except in the rare event of its having become malignant. On section the tumor is solid or cystic but usually the latter. The spaces are filled with mucoid or turbid fluid and are lined by shaggy walls covered with delicate papillary projections. Microscopically the tumor consists of tall columnar epithelium supported by a lymphoid stroma with active germ centers. The epithelium lines the cysts, clothes the papillae and in the solid areas forms small glandular acini in the midst of the lymphoid tissue. Both constituents appear to participate in the neoplastic process. Of the histogenetic hypotheses suggested, the most acceptable is that which refers the origin of the tumor to the epithelium of the salivary duct and lymphoid tissue abnormally blended during development.

FROM THE AUTHORS' SUMMARY.

MIXED TUMORS OF THE FACE AND PALATE. R. FRANSSEN, Ann. d'anat. path. **11**:275, 1935.

In a period of ten years the laboratory of the School of Medicine of the Dutch East Indies (Surabaya) received a comparatively large number of mixed tumors of the face and palate. There was a total of fourteen as follows: palate, three; lips, two; cheek, seven; upper jaw, one; orbit, one. Twelve of the fourteen tumors were in natives. During the same period forty mixed tumors of the salivary glands were encountered.

PERRY J. MELNICK.

BILATERAL TUMORS OF THE ACOUSTIC NERVE AND NEUROFIBROMATOSIS. L. VAN BOGAERT, Ann. d'anat. path. **11**:353, 1934.

Three cases of bilateral tumor of the acoustic nerve are reported. In two of these the tumor was associated with neurofibromatosis. In one of the latter cases this association was pronounced: both parents of the patient and various members of their families were found to have some of the features of Recklinghausen's disease. Histologically, the authors believe, these cases of tumor of the acoustic nerve are instances of schwannoma. PERRY J. MELNICK.

STUDY OF THE SARCOMA OF MICE. A. BESREDKA and L. GROSS, Ann. Inst. Pasteur **53**:341, 1934.

Finely divided sarcoma could be transmitted to mice by all routes, but when intraperitoneal or intracutaneous injections were used multiple large metastases occurred. By mouth only one positive result was secured, but by rectum results were more certain. The blood and organs of animals recently inoculated contained the pathogenic principle, and the supernatant fluid of a centrifugated suspension of such tissue, although showing no cells microscopically, gave rise to a tumor. The activity of the sarcoma was destroyed at 40 C. in four hours and did not resist desiccation or prolonged (three days) holding at laboratory temperature. Shaking with glass beads for several hours rendered the principle inactive. Ablation of the tumor seemed to render an animal more susceptible, but reinoculation of an animal with a sarcoma suggested abnormal resistance. The working hypothesis is advanced that a delicate living agent is responsible for the sarcoma, the latter resulting simply as a defensive reaction. FROM THE AUTHORS' CONCLUSIONS.

CUTANEOUS CARCINOMA AFTER TRAUMA. E. DELANNOY and J. DRIESSENS, Ann. de méd. lég. **14**:828, 1935.

A man at the age of 36 had a carcinoma developing in the scar from an injury sustained twenty-seven years previously.

CUTANEOUS CARCINOMA FOLLOWING INJURY. M. DUVOIR and A. ABECASSIS, Ann. de méd. lég. **14**:833, 1935.

A carcinoma developed within two months at the site of lodgment of a small piece of copper wire under the skin of the hand.

CHONDROMA AND TRAUMATISM. M. DUVOIR and L. POLLET, Ann. de méd. lég. **14**:837, 1935.

A chondroma developed on the left humerus of a man who had received repeated injuries in the region of its origin, the first at the age of 11 years. Definite symptoms were not observed until the age of 47, after several subsequent injuries.

Medicolegal Pathology

SUDDEN DEATH DUE TO HEMORRHAGE INTO SILENT CEREBRAL GLIOMAS. OSCAR T. SCHULTZ, Am. J. Surg. **30**:148, 1935.

A previous study revealed that from 49 to 59 per cent of all deaths reported to three medical examiners' offices and two coroners' offices were due to natural causes. It is usually the suddenness of such deaths that make their investigation necessary. Cardiovascular disease, including hemorrhage, is by far the most frequent cause of sudden death. The most common form of fatal hemorrhage is that which occurs in the brain as a result of vascular disease. A rare form of intracranial hemorrhage is that which results from disruption of the vessels of a previously unrecognized tumor of the brain. The clinical signs and symptoms are those caused by the hemorrhage. Death may occur within a few hours after

the onset of such symptoms. Three cases of fatal hemorrhage into a silent glioblastoma of the brain are presented. With the sudden onset of symptoms of intracranial hemorrhage, the relative youth of the patient as compared with the age of those in whom apoplexy most often occurs may help in reaching the correct antemortem diagnosis of hemorrhage into a tumor of the brain.

From the Author's Summary.

Delayed Death from Pulmonary Embolism. M. W. Shulman, Am. J. Surg. **30**:342, 1935.

Two cases of massive pulmonary embolism are reported in which the patients lived seven days after release of the thrombus. At autopsy they showed almost complete occlusion of the pulmonary arteries and their larger branches. In the first case the condition was a result of stasis in the femoral veins plus infection. In the second case the condition was a result of stasis alone.

(Max Lederer). From the Author's Summary.

Structural Changes in the Central Nervous System in Poisoning with Ammonia. I. G. von Gazekas, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:102, 1935.

Both rabbits and cats show structural changes in the brain after poisoning with ammonia. The changes are similar to those observed in human material. The vessels have swollen walls, fatty changes in the endothelial cells and perivascular cell accumulations; as a consequence perivascular hemorrhages, edema and softening occur. The glia fibers are swollen. The ganglion cells show degenerative changes, especially in the medulla, the cerebellum and in the horns of Ammon.

Spectrographic Demonstrataion of Metal Particles in Electrical Contact Zones. T. Schmidt, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:164, 1935.

Skin from the inner side of the thigh of bodies of persons who had recently died was subjected to electric current of 220 volts and 3 to 4 amperes. Direct and alternating currents were passed through copper or zinc electrodes for intervals of two, five, ten and twenty seconds. With both types of current alterations in the skin were similar to those noted after death from electric shock. With direct current the amount of metal particles deposited in the skin by the electrodes increased as the time of the applied current was increased. With galvanic current metallic deposits occurred deep in the skin when the positive pole was applied but were more superficial when the negative pole formed the contact.

Frozen sections of the skin subjected to the currents were air-dried, studied spectrographically and ashed to determine their metal content. Electrolytic recovery of metal from extracts of the skin was attempted with commercial carbon electrodes but led to conflicting results. Such electrodes contained traces of the metals the recovery of which was attempted. A pure gold electrode was necessary for the minute determinations attempted. The impregnation of the skin with zinc was always more marked than that with copper, a fact apparently explained by a difference in ionic activity.

The results of this work supply a standard for determining the type, duration and direction of an electrical current causing death. The tests were carried out on 1,000 specimens of skin.

George Rukstinat.

Society Transactions

LOS ANGELES PATHOLOGICAL SOCIETY

Regular Meeting, June 11, 1935

A. G. Foord, *President, in the Chair*

J. W. Budd, *Secretary*

Osteogenic Sarcoma in a Fibro-Adenoma of the Breast. Ludwig Lindberg.

A white woman, a tripara, when about 51 years of age noticed a definite lump in the left breast. This diminished in size and remained inactive. Fourteen years later an injury to this breast produced pain, swelling and discoloration lasting several days. Two and a half years after the injury two tumors began to grow. The patient was then 69 years old.

Examination revealed a growth 7 by 7 cm. in the outer upper quadrant of the left breast, not fixed to the deep fascia or to the skin; the skin over the tumor was erythematous. In the axilla were three enlarged lymph nodes. An x-ray film of the chest showed nothing that was abnormal.

The tumor was removed by electrocautery preceded and followed by x-ray radiation; the axillary glands were treated by implantation of radium.

The tissue removed consisted of a firm oval tumor, 7 by 6 by 4 cm., which on section resembled a fibromyoma of the uterus. On one side, within a capsule of compressed fibrous tissue, was a reddish-yellow area, 2 cm. in diameter. Microscopically, the larger part of the tumor was a fibrous pericanalicular and intracanalicular fibro-adenoma. The small portion showed areas of myxomatous tissue, cartilage and osteoid trabeculae separated by a tissue of spindle-shaped fibroblasts. This tissue contained giant cells with deeply staining cytoplasm and from 5 to 20 nuclei. The fibroblasts varied in size and shape, had lost some of their polarity and showed hyperchromatic nuclei, occasionally 2 or 3 nucleoli and an occasional mitotic figure. The pathologic diagnosis was osteogenic sarcoma, grade 1, in a fibro-adenoma of the breast.

About forty tumors of the breast containing cartilage and bone, with eighteen different names, have been recorded in the literature. The clinical diagnosis was usually adenocarcinoma, and radical mastectomy was performed. Of these tumors, thirteen were benign and eighteen were malignant; six produced metastases, usually to the lungs. Nine patients died and four recovered. There was practically no follow-up record in twenty-seven of the cases; the records covered a postoperative period in the others of from a few days to fifteen months.

Intestinal Lesions in Congenital Syphilis. Albert F. Brown.

A premature white infant girl born of a syphilitic mother died about one hour post partum. At necropsy pneumonia alba associated with purulent foci (sterile bacteriologically) was observed. Numerous firm adhesions bound the loops of bowel together and to the pelvic viscera. When the adherent surfaces were cut apart there were left on the peritoneal surfaces thick indurated yellow granular plaques. In the intestinal lumen, the mucosa beneath the peritoneal plaques presented transverse ulcers, 8 by 20 mm., with green indurated bases and sharp straight mar-

gins. The lesions were in two groups, one in the lower part of the ileum, the other at the lower limit of the jejunum. Histologically, the ulcers were gummas, with necrosis extending through all the coats of the bowel. The peritoneal aspect was walled off by a thick layer of granulation tissue which contained miliary gummas. The inflammatory changes about the small vessels were particularly severe. In the muscle coat were dense, abscess-like collections of neutrophils. The center of such an area showed early disintegration of the muscle fibers.

Immense numbers of spirochetes were found in all parts of the tissue except the necrotic areas. The muscle coat was literally "black" with the organisms, which lay in orderly parallelism among the muscle fibers. In the abscess-like areas, however, the spirochetes were relatively scarce.

The description of the lesions agrees with the reports summarized by D. Y. Ku *(Virchows Arch. f. path. Anat.* **280**:852, 1931). The transverse gummatous ulcers were similar to those found in the rare cases of acquired intestinal syphilis (Tuttle, H. K.: *Surg., Gynec. & Obst.* **55**:518, 1932.)

Formerly such abscesses in the intestinal muscle have been explained as an acute reaction to an especially heavy spirochetal infection. In this instance, however, the organisms in the suppurative areas were conspicuously fewer. The same is true of the purulent foci in the lungs. In both intestine and lung the center of attraction for the masses of neutrophils was apparently the necrotic tissue, which was evidently the sequel of the syphilitic obliterating arteriolitis.

Intestinal involvement is reported in the German literature as occurring in from 5 to 12 per cent of cases of congenital syphilis. This case is the only one recorded among 13,000 autopsies including approximately 60 cases of congenital syphilis, at the Los Angeles County Hospital.

MALE PSEUDOHERMAPHRODITISM. O. I. CUTLER.

A white housewife, 52 years of age, came into the hospital complaining of hemorrhoids and pain in the groins which had been present off and on for years. She had never menstruated but thought that she had had menopausal symptoms about three years before. She had been a widow four years. She stated that her sexual life had been normal and satisfactory both to herself and to her husband.

Physical examination revealed what appeared to be bilateral inguinal hernias. The vagina was short. No uterus or uterine cervix was palpable. A small mass in front of the vagina was palpated, which may have been a prostate. The breasts were small.

At operation on the hernias, testes-like objects were present in the sacs. With the testis in each sac were small cysts. Blood vessels led from the testes to points under the peritoneum at the sides of the pelvis. The broad ligaments and the uterus were absent.

Closer inspection of the testes showed a mass grossly resembling epididymis at the hilus of each testis. Sections of these masses showed smooth muscle bundles but no epithelial elements. Tubules could not be teased from the cut surfaces of the testes. Sections showed abundant edematous stroma in which were many tiny tubules having minute or no lumens, resembling those of the fetal testis. Large masses of Leydig cells were present in the interstitial tissue.

The condition was that usually classified as male pseudohermaphroditism, since the patient externally appeared to be a female but possessed testes and had no female internal genitalia.

CORPUS LUTEUM TUMOR. REPORT OF A CASE. O. I. CUTLER.

This report is being published in full in the *American Journal of Obstetrics and Gynecology.*

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Nov. 26, 1935

WILLIAM C. VON GLAHN, *President, in the Chair*

IRVING GRAEF, *Secretary*

MALIGNANT TERATOMA OF THE BLADDER. ABOU D. POLLACK (by invitation).

A 72 year old man on whom a suprapubic operation was performed for the removal of a hypertrophied prostate died one week postoperatively with ascending pyelonephritis and bronchopneumonia. Histologic examination of the prostate revealed simple fibro-adenoma. At autopsy, a primary teratomatous tumor was found in the neck of the urinary bladder. Pulmonary metastases were present. Histologically, the tumor presented malignant adenomatous and mesenchymal tissue elements, including nests of embryonal cartilage.

ADENOCARCINOMA OF THE RECTUM, SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL AND CHRONIC TUBERCULOUS PELVIC ADENITIS. JAMES R. LISA.

A Negro, 37 years old, had had perineal fistulas for ten years. During the last two years a rectal stricture developed, followed by bilateral enlargement of the inguinal and femoral glands. Biopsy of the pararectal tissues revealed a chronic granulomatous lesion. The Frei test was positive. On several occasions Wassermann and Kahn tests of the blood were negative. During the last few months he lost considerable weight.

The autopsy disclosed a large pelvic abscess lined by tumor masses. The entire pelvic colon was destroyed. The lesion was sharply delimited by the pelvic peritoneum. Microscopic examination revealed adenocarcinoma of the pelvic colon with metastases to the right and left femoral glands, right iliac gland and liver, squamous cell carcinoma of the anal canal with metastases to the left femoral glands, and chronic tuberculosis of the right and left femoral, the right inguinal and the right iliac glands.

DISCUSSION

NATHAN CHANDLER FOOT: I should like to ask Dr. Lisa what interpretation he puts on the tubercle bacilli in the second type of lesion which apparently is quite typical lymphogranuloma. I do not know what interpretation he should put on it; I am just curious to know what one he does.

JAMES R. LISA: I failed to mention one point: The clinical diagnosis was lymphogranuloma inguinale. The only interpretation I could put on this after seeing the sections in which the tubercle bacilli were definitely limited to these areas was that it was not lymphogranuloma inguinale but a tuberculous lesion. There is the possibility that this man had lymphogranuloma and that a succeeding lesion destroyed all evidence of the preexistent lymphogranuloma. There is another possibility: that the Frei test may have given a false positive result. One can simply hazard one's opinion as to whether it is a false positive result or whether the patient had lymphogranuloma inguinale.

M. F. WIENER: Does Dr. Lisa assume that there are multiple points of origin of the neoplastic process? There were an adenocarcinoma and a squamous cell carcinoma, and I want to know whether that is merely metaplasia.

JAMES R. LISA: Because of the two distinct types of carcinoma I believe that there must have been multiple foci of origin. That is one point in its favor. Another is the sharp localization to the pelvis, nothing appearing above the pelvic peritoneum. I believe that is evidence that some long-standing chronic irritation must have been present in the pelvis to give rise to two distinct types of pelvic carcinoma.

MULTIPLE OSTEOGENIC SARCOMA. GERTRUDE SILVERMAN (by invitation).

This article was published in full in the January number, page 88.

DISCUSSION

IRVING GRAEF: Were the parathyroid glands examined in this case? Was there any evidence of metastatic calcification in the viscera?

BURR ROYCE WHITCHER: What kind of blood picture did the patient show? Was there marked anemia?

GERTRUDE SILVERMAN: The blood picture was absolutely normal; there was no anemia; the white cell count and the differential count were normal.

BURR ROYCE WHITCHER: Was there involvement of the hematopoietic system in the bone marrow?

GERTRUDE SILVERMAN: The blood-forming elements were not everywhere replaced, which probably accounts for the normal condition of the blood.

The parathyroids were not examined on account of the limitation of the autopsy, and there were no desposits of calcium.

OBSERVATIONS ON LYMPHOGRANULOMA VENEREUM. BORRIS KORNBLITH (by invitation).

Eighty cases in which the Frei intradermal reaction was positive are reported from the laboratories and clinical departments of Mount Sinai Hospital. The lesions fall into three distinct groups according to their presenting symptoms and signs: (1) those involving the inguinal glands, (2) those involving the anus and rectum and (3) chronic genital lesions.

An attempt is made to correlate the histologic observations in all three groups and put them on the basis of a single disease. The histologic lesion in the inguinal nodes, although not pathognomonic, is considered suggestive and sufficiently characteristic for diagnosis. In twelve of fourteen biopsies of inguinal nodes such a lesion was found. The lesion consists of an inflammatory nodule having a peripheral shell of epithelioid cells arranged like a palisade. The central core is filled with inflammatory elements. These include polymorphonuclear leukocytes, lymphocytes, plasma cells, histiocytes and nuclear débris, free or engulfed by histiocytes (gamma bodies). Giant cells of the Langhans type may be present in the peripheral zone later in the disease. As the disease progresses the center undergoes necrosis, while in the periphery accumulations of fibroblasts and plasma cells dominate the picture. Autopsy material from two cases is included.

Histologic examination of the pelvic glands showed lesions identical with those in the inguinal glands. The glands involved were affected as long as from three to six years previous to their examination.

The characteristic histologic picture of the Frei intradermal reaction is reported for the first time. The skin lesion of the Frei test in many ways resembled the characteristic lesion in the lymph nodes. Histologically the skin lesion likewise resembled the acute primary lesion on the genitalia.

It was thus observed that identical histologic features were present throughout all of these conditions, the inguinal, pelvic and genital lesions and the cutaneous Frei reaction. All of these associated clinical entities now find a common histologic correlation with their clinical counterparts.

The histologic features of the punch biopsy specimens of the rectal lesions and chronic genital lesions by themselves, however, were found inadequate for making a specific diagnosis except as they helped to exclude other known pathologic lesions, such as syphilis, tuberculosis and carcinoma. This is consistent with the evolution of the disease. The conditions in the rectum are secondary and reveal changes due to chronic stasis and inflammation. The characteristic lesions are present but out of reach in the pelvic glands.

An attempt to transfer the disease to guinea-pigs resulted in uniform enlargement of the inguinal glands in all cases. The lesions in these glands, however, showed nothing more than hyperplasia of all the lymphoid elements.

Unusual cases of the disease are included: (1) the case of an 8 year old girl with a primary lesion in the rectum; (2) that of a patient who presented generalized lymphadenopathy with hepatosplenomegaly; (3) two cases in which there was fever of unknown etiology; (4) two partner cases.

An attempt at vaccination against the virus is considered advisable and has proved helpful in treatment. All other direct methods were found inadequate.

DISCUSSION

ROBERT T. FRANK: Dr. Kornblith has given a good picture of the disease based on a thorough study of a comparatively large group of cases. The first case that I saw, one of typical esthiomene, was seen thirty years ago; Dr. Sigmund Pollitzer, the dermatologist, sent the patient to me for investigation and possible therapy. I need not tell you that my therapeutic efforts were of no avail. It is amazing to see how in the short course of six years this disease has been so thoroughly elucidated. I think the main factor in this was the discovery of the Frei test. I have seen some of the cases that Dr. Kornblith described, and, while I am willing to acknowledge that the Frei test makes it easy to recognize the condition, there is at present a huge incidence of this disease in New York City, largely due to the influx of many colored people from the South and from Puerto Rico. Dr. Kornblith mentioned the child who was infected as a result of the carelessness or ignorance of her mother. The significance of New York's rapidly spreading focus of infection is so great that either this week or next the Department of Health is going to make the disease reportable, and unless great care is taken in isolating the persons who have it and who are often of a very low group in the population, it is going to become a serious problem.

The chronicity of the infection is such that in the later stages it is often complicated by carcinoma. In this series, at least two patients have shown this combination. Of course, the Frei test is a particular boon because it now enables one to separate cases of syphilis from those of true lymphogranuloma inguinale.

ARTHUR WILLIAM GRACE: At the New York Hospital the attempt to correlate the histologic picture with the Frei test has not always been successful. About two years ago a man of about 60 was observed who had a lump in the left femoral region which he said had appeared twelve years before, had persisted for these twelve years, had not become much smaller or larger during that time, and was not particularly painful. He was brought into the hospital for a hernioplasty, and at the same time he wished to have these glands removed, largely for the cosmetic effect. Some pus was found in them, which was sent to the bacteriologist, and a portion of the tissue was sent to Dr. Foot, who reported that the histologic picture was much like that of lymphogranuloma inguinale and requested that a Frei test be made. A Frei test was made. At that time only the human antigen was available, which was not particularly good material, but the Frei test was made with that material and the result was completely negative. The man left the hospital and was not seen for two years. He went West and remained there. Finally he came back, and the Frei test was performed on him again, some quite strong mouse brain antigen being used. Three antigens were tried, and with not one of them was the result positive. One has here, then, a case which was identical histologically with proved cases of lymphogranuloma inguinale, and yet the Frei test did not indicate the disease.

The second case was that of a woman of 30. She came in with generalized lymphadenopathy and slight pyrexia. She had a relative mononucleosis of from 16 to 20 per cent. Her total white cell count was not high. One of the enlarged glands was taken out for section. The diagnosis was rather obscure. Again the histologic report was suggestive of lymphogranuloma inguinale, and Dr. Foot requested that a Frei test be made. The mouse antigen was by then well developed,

The Frei test was made on this woman repeatedly and again the results were negative. Since that time it has been felt that there is not a 100 per cent correlation between the histologic picture in the inguinal glands and the Frei intradermal reaction, and as it is thought wiser at the moment to rely on a positive Frei test for the diagnosis of lymphogranuloma inguinale the lesions in these two patients are not regarded as representing lymphogranuloma inguinale but as having some other etiology.

I should like to ask about the genital cases which Dr. Kornblith showed, those in which there were old lesions on the genitalia. He mentioned looking for Ducrey's bacillus. I wonder whether he tried the dmelcos test. I have found that a particularly useful test. The material is difficult to obtain in this country, but if one has a friend in Canada one can get some. It is an intradermal test and is performed with 0.1 cc.; the positive reaction is very evident. I wonder whether that test may not be performed in the genital cases which Dr. Kornblith showed.

MARION B. SULZBERGER: The histology and the clinical aspects of lymphopathia venereum have been so well discussed by Dr. Kornblith that it is unnecessary to go into further details on these points. It might be interesting to some of the gentlemen who perhaps wonder why a skin specialist gets up to discuss this paper to say something of the development of the Frei test. Dr. Frei is a dermatologist, and this disease was primarily studied by dermatologists. I was fortunate enough to be working in the clinic at Breslau with Frei in 1928-1929. He had described his test in 1925, and as a careful worker he was anxious to know something about the specificity of the reaction. He therefore made control tests on a large number of persons not affected with any of the inguinal manifestations of this disease. When he had done a large number of such tests he found that he was getting positive reactions in a certain small number of persons who had not had inguinal buboes. On analyzing these presumably false positive reactions he found that they were all either in women with esthiomene or in women with rectal strictures of the type which you have heard described or in men with no inguinal adenopathy but with rectal strictures. He was somewhat at a loss to explain these at first seemingly false positive reactions until he managed to trace the male partners of the women who had given positive Frei reactions. In almost every instance he was able to demonstrate that the partners either had or had had inguinal manifestations or gave a positive Frei reaction. It was in this manner that the concept of this disease was enlarged to embrace the noninguinal manifestations which you heard of in these cases of rectal stricture and of ulcerative and/or elephantiasic processes of the female and male genitalia, as well as in cases of certain skin and other manifestations.

The immunologic side could be made the subject of a lengthy treatise, but I shall say only a few words on this subject. In Breslau we thought from the beginning that we had shown that the Frei test was to be considered specific. Subsequently some observers denied this specificity. But further experience has shown that this test is perhaps the most specific of all intradermal tests that are performed. In spite of this fact there are undoubtedly some cases of seemingly typical clinical lymphopathia venereum with a typical histologic picture in which the Frei reaction is negative. I am, however, inclined to disagree with Dr. Grace that the Frei test must be the ruling criterion and that a negative test excludes the diagnosis of lymphopathia venereum. I should say that some of these cases in which the Frei test is negative may nevertheless be cases of lymphopathia venereum, and that the diagnosis must be left open. Theoretically this holds true for all immunologic changes in infectious diseases. For instance, the concept of a positive anergy in tuberculous persons shows that not all tuberculous persons give a positive tuberculin reaction. One must postulate the existence of such an anergy in leprosy, syphilis, etc., and perhaps in lymphopathia venereum also. The question could be answered by making extracts of tissues of those who fail to react and

cross-testing the extract on those who have given positive reactions. I have seen two persons with typical lymphopathia venerea in whom the Frei test repeatedly gave negative results with many Frei vaccines, but the pus or the extracts from their tissues elicited positive Frei reactions when injected into persons who had given positive Frei reactions.

SOLOMON WEINTRAUB: I have been much interested in this subject because at Harlem Hospital, where 90 per cent of the patients are colored, we have seen a large number of cases of this type. As far as I can recall, the observations in those cases agree with the statistics that have been presented here. No rectal strictures were seen in any of the male patients; strictures were observed only in colored females. A number of specimens are available at Harlem Hospital for inspection.

The sections were stained for tubercle bacilli, spirochetes, and Leishman-Donovan bodies, but it was not possible to find any of these organisms. I am anxious to know Dr. Kornblith's findings in regard to Leishman-Donovan bodies.

DAVID BLOOM: The Frei antigen may give a false positive reaction if it is contaminated. A few weeks ago in Bellevue Hospital I saw a woman 21 years old whose rectal trouble was diagnosed by some as stricture due to lymphogranuloma venereum, because of her age and a positive Frei test. I saw her about one week after the test was made, and there still were pigmentation and scarring in place of the inoculation. Because of a roentgenogram made following a barium sulfate enema which did not show the usual picture of stricture of the rectum caused by lymphogranuloma venereum, and because of the short duration of her symptoms, I doubted the diagnosis of lymphogranuloma venereum. When the patient was on the operating table, carcinoma of the rectum was found. The Frei test when repeated with fresh human antigen and mouse antigen proved absolutely negative. It is important, therefore, to be sure that the antigen is not contaminated. This contamination occurs readily, for the material is a good soil for the growth of pyogenic bacteria.

I wish also to state that in an extensive experience with lymphogranuloma venereum and its strictures at Bellevue Hospital very good results have been obtained from the use of antimony and potassium tartrate. This seems to affect the inflammatory and edematous factor of the strictures beneficially, so that the symptoms abate considerably or disappear.

EDWIN BEER: Apparently it is fairly universally conceded that the Frei test is specific and diagnostic, and the experience on the surgical service at Mount Sinai Hospital seems to bear this out. These conditions surely are not new. They have been unrecognized by clinicians and by pathologists. I have seen any number of typical chronic inguinal buboes with suppurating centers at Bellevue and Mount Sinai Hospitals in the last thirty years and have always been under the impression that they were in some way connected with a mild long continued coccal infection. They all show cocci in smears when they rupture. The same observation is made in cases of stricture of the rectum and esthiomene. The high stricture of the rectum in women has been considered by most clinicians as quite specific, or gonorrheal. I can remember operating on a whole series of these strictures by plastic surgery, and the end-results were deplorable, because the strictures reformed, the lesions being perirectal and involving only late the muscularis of the rectal wall.

There is one interesting observation which I have made, if I can judge from a single experience, and that is that one cannot readily infect the human being by contact. In a case in which I excised a group of inguinal glands which were suppurating, the assistant's hand was too big and got in the way of the knife, and though he had an elliptic cut in the web of his thumb, he did not get infection from this.

I think what Dr. Frank said is important, that the Department of Health is going to make this a disease concerning which the health officer is notifiable, because apparently it is definitely on the increase in this particular neighborhood.

BORRIS KORNBLITH: At Mount Sinai Hospital we have had an experience similar to that of Dr. Grace in the case of a nurse with lesions in the axillary glands which were considered very suggestive of the disease. We had another case of a biopsy of an abdominal gland which was likewise considered to show typical lymphogranuloma. In both patients the Frei test was negative. One died before there was an opportunity to repeat the test with another antigen, and the other one could not be followed. The antigen for the dmelcos test which Dr. Grace mentioned is difficult to obtain in this country, and on that account we have not used it.

Dr. Sulzberger is modest. He was the first one to introduce the Frei test in this country. He mentioned partner cases. To get such cases under observation leads one into many obvious personal and social difficulties. In spite of that some cases of this type have been seen in which the husband or the wife voluntarily brought in the mate. This offered an opportunity to study the possibility that the disease is transferred to the offspring. It was found that if the husband and the wife were infected, even before the children were born, the Frei reaction of the child was not necessarily positive. There were two families in which the children gave negative results in spite of the fact that both the mother and the father showed positive Frei intradermal reactions.

In reply to Dr. Weintraub's question about Donovan bodies, we looked for them and were unable to find any.

Antimony and potassium tartrate was used and found inadequate in treatment. Fuadin was also tried and found unsatisfactory in a number of cases. The favorable results at Bellevue Hospital in the treatment of rectal lesions with antimony and potassium tartrate have been reported by other clinicians. It is difficult, however, to evaluate any straightforward report when one reviews these cases. They say that antimony and potassium tartrate is good, but they do not say how good it is. We have tried other forms of treatment in these cases, the rectal as well as the inguinal cases, and found that symptomatically all of the patients improved by one method of treatment or another. The patients with the inguinal lesions may appear cured but may very well acquire a stricture ten or fifteen years afterward. Under treatment with the Frei antigen the patients with rectal lesions appear better physiologically, but anatomically the lesions are fixed. The local symptoms clear up, but the pathologic process remains as active as before treatment was begun.

PRIMARY SARCOMA OF THE BREAST. SEATON SAILER.

In the surgical files of the pathological department of St. Luke's Hospital fourteen primary sarcomas of the breast have been recorded over a period of thirty-five years. They formed 0.75 per cent of all the malignant tumors of the breast (1,847 primary carcinomas of the breast) operated on during this period. All of the sarcomas of the breast occurred in women. The right and left breasts were affected equally. The average age of onset was 51 years, five cases occurring between the fifth and sixth decades and three between the third and fourth decades. These tumors were divided into simple and complex types, the former comprising by far the greater number. Five of these were classified as spindle cell fibrosarcoma and showed the most uniform histologic appearance. One of the patients with spindle cell fibrosarcoma is alive and well today, nine years after radical removal of the affected breast. Two tumors were classified as fibromyxosarcoma and one as neurogenic. One patient in the former group first complained of a purulent discharge from the nipple two years prior to admission. Simple mastectomy was performed a year after her initial complaint; recurrence was prompt, and on admission a large unencapsulated grayish mucoid mass, 7 by 5 cm., was removed and the underlying pectoral muscles and axillary glands resected. The patient showed local recurrence and metastases in the lungs within a few weeks. Three tumors were classified as polymorphocellular fibrosarcoma and were composed of

large and small spindle-shaped, irregularly round and polyhedral cells. Many large tumor cells showing varying degrees of nuclear and cytoplasmic malformation were scattered throughout. One of the patients showed a local recurrence two months after removal of a circumscribed tumor measuring 3 by 1.5 cm. and died six months later from pulmonary metastases. Three tumors were classified as belonging to the complex type. One of these was a chondromyxosarcoma which had been noticed four years before admission by a 68 year old white woman. During the last year and a half the tumor grew rapidly and filled the entire breast. It was composed of small islets of hyaline cartilage disseminated through a myxomatous and fibrous stroma. Another tumor designated as an osteochondrofibrosarcoma occurred in a white woman 59 years old and was noted six weeks prior to her admission. Skeletal x-ray films showed no lesions. A tumor measuring 4 by 3 cm. was removed at operation and found to be composed of well formed bone, osteoid tissue, hyaline cartilage and interlacing bundles of elongated spindle cells. The patient is alive and well five months after the operation. The last case was one of rhabdomyosarcoma, occurring in a colored woman of 38 years. A node the size of a bean had been noted two years before and was removed at the end of the first year. It recurred seven months later at the site of the scar. On admission to St. Luke's Hospital the patient was dying and showed signs of intestinal obstruction. Autopsy revealed multiple metastases throughout the lungs, liver and retroperitoneal nodes. Four pedunculated tumors were present in the intestine, involving the stomach, jejunum and ileum. An intussusception was caused in the latter near the ileocecal valve by a large tumor. Microscopically the original tumor of the breast and *all* the metastatic lesions were composed of elongated striated muscle fibers, myoblasts and small irregularly round and polyhedral cells. Only one tumor of this type has previously been reported as occurring primarily in the breast (Billroth: *Virchows Arch. f. path. Anat.* **18**:69, 1860).

DISCUSSION

PAUL KLEMPERER: Did Dr. Sailer find some cases in which an adenomatous structure was present within the sarcoma?

SEATON SAILER: I have not seen a single case that could be classified as one of adenosarcoma. In all the cases the sections showed were the most representative.

PAUL KLEMPERER: I asked the question because in recent years I have twice had the opportunity to observe tumors of the breast which presented very great difficulties in diagnosis, particularly as to advising the surgeon what to do. These were fibro-adenomas, well encapsulated tumors, in which the stroma showed definite atypism and mitotic figures. It is very difficult on frozen section to make a definite diagnosis in such cases, and in both of the instances I mention we were unpleasantly surprised when in the paraffin sections we noticed the atypism and were forced to say that we might have been mistaken in considering the tumor a benign fibroadenoma. In both cases there was a rather wide excision in spite of the fact that the tumors were well encapsulated, and nothing further was done. One case was observed five years ago, and the patient is well. I wonder how one should consider a case in which one recognizes at the operating table that it belongs to this questionable borderline group, or that of early adenosarcoma.

ALFRED PLAUT: Did the material at St. Luke's Hospital include any cases of isolated lymphosarcoma?

SEATON SAILER: We have not had any case in which an isolated lymphosarcoma was found. In one case of myeloma a large mass was present in the breast, but at the same time numerous metastatic nodules were found throughout the system, and this case was not included. The only case of pure lymphosarcoma was one that occurred in the axillary region, and it was not included.

MENDEL JACOBI: I should like to add to Dr. Sailer's experience my own. In about two hundred cases in the last six years I have observed three sarcomas of the breast, and all were in males. Two were pleomorphic sarcomas; one of the

patients was lost sight of after the mastectomy; the other died three days after the mastectomy, and while it was possible to get only an autopsy limited to the chest and axillary lymph nodes, and while the original tumor was well encapsulated, I was able to find some metastases by direct extension in the pectoral muscle, and a very questionable one in the axillary lymph nodes.

Concerning the question which Dr. Klemperer raises, I have had difficulty in advising surgeons on frozen sections and even on paraffin sections. I recall a case five years ago in which I suggested that the tumor was an atypical fibro-adenoma, and on the basis of that the surgeon did an extensive operation. Four and a half years later the patient came back with metastases in the lungs. A reexamination of the sections did not cause me to change my original diagnosis and reclassify the tumor as a sarcoma.

Book Reviews

Agents of Disease and Host Resistance Including the Principles of Immunology, Bacteriology, Mycology, Protozoology, Parasitology and Virus Diseases. By Frederick P. Gay and Associates. Price, $10. Pp. 1,581, with 212 figures, 6 color plates and 61 diagrams. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This large book is the product of an ambitious collaborative project to review the present knowledge of the causation of disease, with special reference to the living agents of disease. In the preface the senior author expresses himself as dissatisfied with the fragmentary accounts of the causes of disease presented to the student early in the medical course. Study of the agencies of disease, he holds, is the first logical step to the understanding of disease in general. "It is this viewpoint that for many years we have presented to our students under the guise of a course in medical bacteriology. . . . We offer now to a larger audience under a somewhat unusual title, in more complete form, a treatise that aims to present the principles of what are properly a series of sciences; namely, bacteriology, protozoology, parasitology, and immunology, to say nothing of certain groups of facts dealing with other disease agencies, particularly those of inanimate nature, that have not been so clearly denominated." With four exceptions, the authors have been in close association in the department of bacteriology in the College of Physicians and Surgeons of Columbia University, and they have tried "to strike a balance between the one-man text and the collected monographs of multiple authorities."

There are sixty-five chapters, which in the table of contents are grouped into twelve parts, but this grouping is not indicated in the text. In the first part Gay discusses the causation, classification and nature of disease in the three short but very good chapters on the development of the present concepts of the nature and causation of disease, on nosology as a basis of etiology and on secondary and intrinsic factors in the production of disease. The second part is devoted to inanimate agents of disease and tolerance. Here are included two extensive chapters on anaphylaxis (Beatrice C. Seegal) and allergy (David and Beatrice C. Seegal), in which all phases of these processes receive competent consideration. Part three deals with the morphology and physiology of living pathogenic agents, particularly bacteria. Gay writes scholarly accounts of the history of bacteriology and of the trends of discovery of the living agents of disease. A comment on variation in bacteria merits quotation: "Diagnostic criteria, based on the invariability of bacteria when observed under a given and specified set of conditions, remain inviolate and as useful as ever. The essential constancy and pathogenic characteristics of each separate species are not affected by this newer appreciation that bacteria have a much more elaborate and complicated life history than we previously knew." The chapter on the nature, form and structure of pathogenic micro-organisms (Richard Thompson) also gives consideration to bacterial variation. The general physiology of micro-organisms receives thorough treatment (Gay and others), and there is a good chapter on disinfection by M. L. Isaacs. Part four, on infection and immunity, consists of a chapter by Gay on infection in general and a chapter on epidemiology by C. W. Jungeblut. Resistance and immunity are the subjects of part five. Natural resistance and acquired immunity to living pathogenic agents, the humoral aspects of natural resistance, the cellular basis of resistance and the phagocytic theory, acquired immunity and lytic phenomena and tissue immunity are subjects of comprehensive chapters by Gay. In the sections on opsonins one misses references to worthy American work on opsonins and intraphagocytic destruction of bacteria. Agglutination and the precipitin phenomenon are handled

competently by James T. Culbertson; antigens and antibodies, by C. W. Jungeblut, Beatrice C. Seegal and L. Buchbinder. Part six covers the pathogenic bacteria and the diseases caused by them. This part alone extends over 600 pages and would make a good-sized book by itself. Of its twenty-two chapters, it may be noted that the ones on streptococci and on the enteric group are by the senior author, whose work on typhoid fever is well known. In the discussion of hemolytic streptococci in relation to scarlet fever and erysipelas, certain observations that the toxins of the streptococci of these two diseases are distinct (Dick, G. F., and Dick, Gladys H.: J. A. M. A. **93**: 1784, 1929. Lehmann: Ergebn. d. inn. Med. u. Kinderh. **40**:633, 1931) do not receive mention and the fact that scarlet fever and erysipelas are distinct and separate diseases is not considered in its bearing on the problem of streptococcic specificity. The comprehensiveness of the treatment in this part is illustrated by the chapter of 69 pages on tubercle bacilli and tuberculosis by M. Maxim Steinbach. The references at the end of the chapter take up 7½ pages. As a rule, the references at the end of the chapters are listed alphabetically according to the names of the authors, the titles to articles in periodicals being omitted. When there are so many references as in this chapter, perhaps it would have been of advantage if the references had been grouped under topics. Syphilis and the other spirochetal diseases are the topics of the seventh part (Theodor Rosebury), and in part eight Rhoda W. Benham devotes 30 pages to an excellent review of pathogenic fungi. Indeterminate pathogenic forms and diseases produced by them are the subjects of part nine, by E. B. McKinley. Here the rickettsiae, the filtrable viruses and the bacteriophage receive full and orderly consideration. Lymphogranuloma inguinale is dismissed too hurriedly; the Frei test is not mentioned. Pathogenic agents of animal nature occupy the 153 pages of part ten. Richard W. Linton writes on pathogenic sporozoa; George W. Bachman on helminths as agents of disease, and William A. Hoffman and James T. Culbertson no arthropods as agents and vectors of disease. The guardians of correct spelling of scientific names will be shocked to see "Endameba" used throughout the chapter on amebiasis. Part eleven (Richard Thompson) reviews diseases of obscure etiology, e. g., glandular fever, erythema nodosum, malignant tumors, diseases of the thyroid gland, certain nervous diseases and other disorders. From the bare mention of epidemic diaphragmatic pleurodynia, also called epidemic myalgia, it is evident that Sylvest's monograph (Epidemic Myalgia, London, Oxford Press, 1934) and the editorial review of the disease in *The Journal of the American Medical Association* (**102**:460, 1934) have escaped the notice of the author. In part twelve, on practical aspects of the diagnosis, prevention and cure of infectious diseases, Gay, Jungeblut and Culbertson write instructively on diagnostic reactions, active immunity and preventive vaccination, serum treatment and prophylaxis, and chemotherapy.

The index of subjects appears to be good and complete. The Shwartzman phenomenon (page 344) has eluded the eye of the indexer. Scattered throughout the book are numerous helpful illustrations in black and white, tables, diagrams and charts. There are also six high-grade colored plates and portraits of a number of persons who figured prominently in the development of the present knowledge of living agents of disease. The book is printed well in clear type. The pages are large, octavo, and the lines are long; when smaller type is used the page is divided into two columns. It is a cumbersome book to handle on account of its bulk and weight.

The book contains an enormous amount of well arranged information. Many chapters are monographic in scope and exhaustiveness. Certainly, the object to deal comprehensively with the causation of diseases has been well achieved, so far as the living agents of disease, their products and the reactions of the host are concerned. The book will serve especially advanced workers in the fields that it covers.

The Wistar Institute Style Brief. A guide for authors in preparing manuscripts for the most effective and economical method of publishing biological research. Prepared by the cooperative efforts of the editors of journals published by the Wistar Institute and the Staff of the Wistar Institute Press. Pp. 169, with 23 figures and 37 plates. Philadelphia: The Wistar Institute Press, 1934.

The aim of this pamphlet is to assist authors in the preparation of papers and thus to facilitate the printing of the periodicals published by the Wistar Institute. While aimed directly at the periodicals of the Wistar Institute, the pamphlet contains much of interest and value for all who are concerned with the preparation and publication of scientific articles. The preparation of articles is discussed under the following heads: the purpose of the article, the title, the general form, the style, the abstract (for the Wistar Institute Bibliographic Service), outline and headings, literature cited, nomenclature, figures and plates, discussion and summary. The directions relative to the manuscript include paragraphs on the paper, writing, care of copy, paging, style, main title, paragraphing, headings, author's abstract, indexing, subsidiary matter, footnotes, extracts, protocols, tables (with illustrations), contents, capitals, orthography, italics, punctuation, references, dates, numerals, literature, heads and subheads and proof. A highly valuable part of this brief is that dealing with illustrations. Here are discussed the originals, magnification and reduction, lettering, grouping and mounting and alterations. This part is illustrated with thirty-seven plates taken from publications of the Wistar Institute. The brief will be of value not only to authors in general but also to editors and printers. It illustrates well the desirability of preparing manuscripts in accord with the style of the periodical to which they are submitted. "At every step, from the receipt of copy by the editor to the actual running of the press, the slightest error, inconsistency, lack of clearness in copy or correction on author's proof causes delay, loss of time, extra and unnecessary handling of a mass of heavy metal and involves extra expense."

Adequate publication with the least expense can be secured only by the intelligent cooperation of author, editor and press. In view of the cost and of the increasing volume of publication, with all its implications, every reasonable effort must be made to reduce the mass of printed matter without loss in essential value. In connection with this phase of scientific publication the question arises whether it is now advisable to print in the references to the literature the titles of articles in periodicals. Has not the time come for a more economic bibliographic practice?

Epidemics and Crowd-Diseases: An Introduction to the Study of Epidemiology. By Major Greenwood, D.Sc., F.R.C.P., F.R.S., President of the Royal Statistical Society, Professor of Epidemiology and Vital Statistics in the University of London, formerly Medical Officer in the Ministry of Health. Price, $5.50. Pp. 409. New York: The Macmillan Company, 1935.

This book is based on instruction given by the author to professional students in the London School of Hygiene and Tropical Medicine, but it is not a textbook with an eye to examinations. The object is to introduce educated persons "interested in some of the larger problems of preventive medicine to the methods of study which have been used and the results which have been attained." There are two parts. The first is concerned with general principles and methods. Beginning with Hippocrates and Galen, the evolution of epidemiology, the study of disease as a mass phenomenon and of the science of statistics is followed through the revival of learning and the age of Pasteur and Galton to modern experimental epidemiology, the artificial immunization of man and the study of nutrition, occupation and psychologic factors in their relation to the health or sickness of a crowd. The second part presents special illustrations: the typhoid group, cholera, typhus, measles, diphtheria, scarlet fever, Edward Jenner and Charles Creighton, the post-jennerian controversy, plague, epidemic diseases of the central nervous system, influenza, venereal diseases, tuberculosis, cancer. While the importance of the statistical method of handling epidemiologic data is stressed, the book can be read

with instruction and pleasure without mastery of high mathematics. The style is enjoyable. The tone is wholesomely critical and sane. Greenwood's opinions and deductions are stated cautiously yet clearly and sometimes amusingly. With respect to cancer, for instance, Greenwood concludes that statistics so far do not warrant any conclusion of general etiologic significance. "The answer to the young lady's question to Babbage, of calculating machine fame: 'Please, Mr. Babbage, if you ask the wrong question, will it give you the right answer?' is still 'No.' Even in his country [England] approximately accurate statistical data of mortality from cancer are a product of less than a generation. The accuracy is still only approximate." The book presents exceedingly well a phase of medicine of value to all who are interested in epidemics and crowd diseases. No one should hesitate to take up this book on the ground that it may be dry and technical.

Annals of the Pickett-Thomson Research Laboratory: Volume X. Influenza (Part II), With Special Reference to the Complications and Sequelae, Bacteriology of Influenzal Pneumonia, Pathology, Edipediological Data, Prevention and Treatment. By D. and R. Thomson. Price, $17.50. Pp. 1557. Baltimore: Williams & Wilkins Company, 1934.

This large volume concludes the summary of the existing literature on influenza undertaken by those indefatigable bibliographers, David and Robert Thomson. It is even larger (917 pages) than the first volume (Part I, 690 pages) on the same subject, the two together (1,557 pages) constituting the most ambitious attempt yet made in this field. The bibliography on influenza at the end of the second volume occupies 101 pages and contains more than 4,500 references. The text is clearly printed and seems astonishingly free from misprints.

One would not expect to find a highly critical and analytic treatment of the enormous amount of material cited in this survey. At most it is a well organized series of abstracts by competent hands, interlarded with lengthy citations from the more important critical reviews and original monographs. Even so, it is a gigantic undertaking and worthy of admiration. Whether such colossal compilations justify the time and labor expended on them is a question to which various answers may be expected. There is no doubt, however, that for many years to come students of the influenza problem throughout the world will be saved much time and labor by being able to consult the full and extensive description of the work of their predecessors given in these volumes. This is a real service to science.

Classical Contributions to Obstetrics and Gynecology. By Herbert Thoms, M.D., Associate Professor of Obstetrics and Gynecology, Yale University. With a foreword by Howard A. Kelly, M.D., Professor Emeritus of Gynecology, Johns Hopkins University. Price, $4. Pp. 265, with 57 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This book consists of fifty-nine selections from classic contributions to clinical obstetrics and gynecology before 1900. Living authors are not included. The selections, all in English, are preceded by brief historical and biographic introductory paragraphs. There are seven chapters, with a discussion of the following subjects: general obstetrics, the course of labor, the pathology of obstetrics, obstetric operations, puerperal infection, pelvic deformities, gynecology. The last chapter deals largely with the great American pioneers in the beginnings of modern gynecology. Four Americans figure in the chapters devoted to obstetrics, namely, John Stearns, who is given chief credit for the introduction in 1807 of ergot in scientific obstetrics; Walter Channing, who first depicted the so-called pernicious anemia of pregnancy in 1842; Marmaduke Burr Wright, who in 1854 described cephalic version, and, of course, Oliver Wendell Holmes, who wrote his great essay on "The Contagiousness of Puerperal Fever" in 1843. The illustrations include fifty-seven portraits, many of which are unusual; facsimiles of pages of famous books, of pictures and instruments. The press work is well done. On page 245 Neisser of gonococcus fame appears as Niesser. The book fully merits the warm welcome given it in the forewood by Kelly.

Books Received

A Geography of Disease. A Preliminary Survey of the Incidence and Distribution of Tropical and Certain Other Diseases. Earl Baldwin McKinley, M.D., Dean and Professor of Bacteriology, George Washington University School of Medicine, and Director of Studies of the Survey. Published as a supplement to The American Journal of Tropical Medicine. Price, $5. Pp. 495. Washington, D.C.: The George Washington University Press, 1935.

Bacteriology in Relation to Clinical Medicine Theoretical and Applied. For Students, Laboratory Workers and Practitioners in Medicine and Public Health. M. N. De, M.B., M.R.C.P. (Lond.), Professor of Pathology, Medical College of Bengal, Calcutta; Bacteriologist to the Government of Bengal; and K. D. Chatterjee, M.B., Medical Registrar, Medical College Hospitals, Calcutta; formerly Research Assistant, Department of Pathology, Medical College, Calcutta. Price, 30 shillings. Pp. 599, with 276 illustrations. Calcutta, India: "Statesman" Press, 1935.

The Patient and the Weather. William F. Petersen, M.D. Volume 1, Part 1. The Footprint of Asclepius. Pp. 127, with 94 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1935.

The Pathogenic Aerobic Organisms of the Actinomyces Group. Dagny Erikson. Medical Research Council, Special Report Series, No. 203. Price, 1 shilling. Pp. 61, with 11 illustrations. London: His Majesty's Stationery Office, 1935.

Medical Uses of Radium. Summary of Report from Research Centres for 1934. Medical Research Council, Special Report Series, No. 204. Price, 1 shilling. Pp. 45, with 6 illustrations. London: His Majesty's Stationery Office, 1935.

Manuel de coprologie clinique. R. Goiffon. Third edition. Price, 28 francs. Pp. 274, with 45 illustrations. Paris: Masson & Cie, 1935.

Localized Rarefying Conditions of Bone as Exemplified by Legg-Perthes' Disease, Osgood-Schlatter's Disease, Kümmell's Disease and Related Conditions. E. S. J. King, M.D., D.Sc., M.S. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Honorary Surgeon to Out-Patients, Melbourne Hospital; Stewart Lecturer in Pathology, University of Melbourne. Cloth. Price, $7.50. Pp. 400, with 70 diagrams. Baltimore: William Wood & Company, 1935.

The Rockefeller Foundation International Health Division Annual Report, 1934. Pp. 235. New York: Rockefeller Foundation, 1935.

A B C of the Endocrines. Jennie Gregory, M.S. With a foreword by Carl G. Hartman, Department of Embryology, Carnegie Institution of Washington. Price, $3. Pp. 126. Baltimore: Williams & Wilkins Company, 1935.

Atlas of Pathological Anatomy. Issued under the direction of the Editorial Committee of the British Journal of Surgery. Compiled by E. K. Martin, M.S., F.R.C.S. Volume II. Price, $15. Pp. 475. Baltimore: William Wood & Company, 1935.

Immunology. Noble Pierce Sherwood, Ph.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. Price, $6. Pp. 608, with 27 illustrations and 8 colored plates. St. Louis: C. V. Mosby Company, 1935.